Docket No.: 029490.0101-US02
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Joseph G. Masterson et al.

U.S. Patent No.: 5,540,938

Issued: July 30, 1996

For: FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

TRANSMITTAL LETTER

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

Dear Sir:

Enclosed are the following items for filing in connection with the above-referenced Patent Application:

1. Fee Transmittal;

2. Request for Extension of Patent Term under 35 U.S.C. § 156 (original plus three copies) together with Exhibits 1-12 (original plus two copies); and

3. Return receipt postcard.

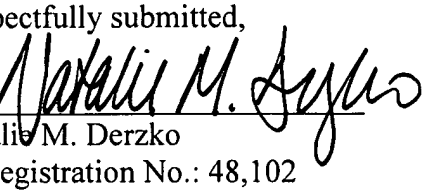
Please charge our Deposit Account No. 50-0740 in the amount of $1,120.00 to cover the required fees. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this

application by this firm) to our Deposit Account No. 50-0740, under Docket No. 029490.00101-US02. A duplicate copy of this paper is enclosed.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 50-0740.

Dated: March 17, 2010

Respectfully submitted,

By 

Natalie M. Derzko
Registration No.: 48,102
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000

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Dated: March 17, 2010

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By _____
Natalie M. Derzko
Registration No.: 48,102
COVINGTON & BURLING LLP
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Washington, DC 20004-2401
(202) 662-6000

PTO/SB/17 (10-08)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no person are required to respond to a collection of information unless it displays a valid OMB control number

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2009

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 1,120.00

Complete if Known	
Application Number	US Patent No. 5,540,938
Filing Date	Issued: July 30, 1996
First Named Inventor	Joseph G. Masterson
Examiner Name	N/A
Art Unit	N/A
Attorney Docket No.	029490.00101-US02

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☒ Deposit Account Deposit Account Number: 50-0740 Deposit Account Name: Covington & Burling LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☒ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
Application Type	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fee ($)	Small Entity Fee ($)	Fees Paid ($)
Utility	330	165	540	270	220	110	
Design	220	110	100	50	140	70	
Plant	220	110	330	165	170	85	
Reissue	330	165	540	270	650	325	
Provisional	220	110	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	52	26
Each independent claim over 3 (including Reissues)	220	110
Multiple dependent claims	390	195

Total Claims	- 20 or HP =	Extra Claims	x Fee ($)	= Fee Paid ($)

HP = highest number of total claims paid for, if greater than 20.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)

Indep. Claims	- 3 or HP =	Extra Claims	x Fee ($)	= Fee Paid ($)

HP = highest number of independent claims paid for, if greater than 3.

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	- 100 =	Extra Sheets	/50 =	Number of each additional 50 or fraction thereof (round up to a whole number)	x Fee ($)	= Fee Paid ($)

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): 1457 Extension of term of patent	1,120.00

SUBMITTED BY					
Signature	Natalie M. Derzko	Registration No. (Attorney/Agent)	48,102	Telephone	(202) 662-5301
Name (Print/Type)	Natalie M. Derzko			Date	March 17, 2010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
INVENTOR Masterson, et al.

Patent No.: 5,540,938

Issued: July 30, 1996

For: FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

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REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, Elan Pharma International Ltd., the address of which is Monksland, Athlone Co., Westmeath, Ireland, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,540,938 (Exhibit 1) granted to Joseph G. Masterson and Michael Myers on the 30th day of July, 1996, for "Formulations and their Use in the Treatment of Neurological Diseases" by virtue of an assignment from the inventors to Elan Corporation, PLC, recorded December 17, 1991 at Reel 005960, Frame 0060 (Exhibit 2), and a further assignment from Elan Corporation, PLC to Elan Pharma International Ltd. (Exhibit 3), recorded July 23, 2008 at Reel 021266, Frame 0957. The '938 patent matured from United States Patent Application No. 08/328,165, filed on October 24, 1994 ("the '165 application"). The '165 application is a

divisional of U.S. Patent Application No. 08/073,651, filed on June 7, 1993, now U.S. Patent No. 5,370,879, and a divisional of U.S. Patent Application No. 07/786,400, filed on November 1, 1991, now abandoned.

The approved product that is relevant to this application is AMPYRA™ (dalfampridine) Extended Release Tablets, referred to herein as "AMPYRA" or "Approved Product."

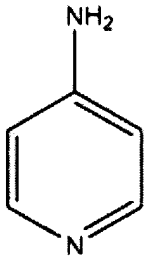
The Marketing Applicant for AMPYRA is Acorda Therapeutics, Inc. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 4.

The following information is submitted by Acorda Therapeutics, Inc., through its duly authorized attorney, Covington & Burling LLP, on behalf of Applicant (see Exhibit 5), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is AMPYRA, an extended release tablet with the active ingredient dalfampridine, available in a 10 mg strength. AMPYRA has been approved as a treatment to improve walking in patients with multiple sclerosis (MS) as demonstrated by an increase in walking speed (approved labeling attached as Exhibit 6). AMPYRA is a potassium channel blocker.

The chemical name of dalfampridine is 4-aminopyridine, with the following chemical structure:



(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

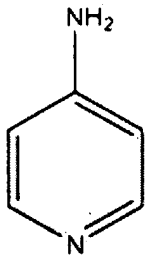
The Approved Product is a drug product that was approved under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 355(b)(1)).

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The Approved Product received permission for commercial marketing or use by the United States Food and Drug Administration (FDA) pursuant to section 505(b)(1) of the FFDCA in a letter dated January 22, 2010. A copy of the approval letter is attached as Exhibit 7.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. § 1.740(a)(4))

AMPYRA is a potassium channel blocker that has been approved under Section 505(b) of the FFDCA as a treatment to walking in patients with multiple sclerosis (MS). The active ingredient of AMPYRA is dalfampridine (i.e., 4-aminopyridine) with the chemical structure:



Neither dalfampridine, nor any salt or ester of this active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act. Indeed, the FDA has granted New Chemical Entity (NCE) status to AMPYRA (dalfampridine), indicating that AMPYRA represents the first approval by FDA of a drug product containing the dalfampridine active moiety.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on January 22, 2010 when the product received permission under 505(b)(1) of the FFDCA and that will expire on March 23, 2010. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on March 22, 2010.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO.: 5,540,938

INVENTORS: JOSEPH G. MASTERSON and MICHAEL MYERS

DATE OF ISSUE: JULY 30, 1996

EXPIRATION DATE: JULY 30, 2013

The expiration date of U.S. Patent No. 5,540,938 ("the '938 patent") is July 30, 2013 based on the following information. The patent application that issued as the '938 patent, U.S. Patent Application No. 08/328,165 ("the '165 application), was filed on October 24, 1994, as a divisional of U.S. Patent Application No. 08/073,651, filed on June 7, 1993, now U.S. Patent No. 5,370,879, and a divisional of U.S. Patent Application No. 07/786,400, filed on November 1, 1991, now abandoned. The last filed application that matured into the '938 patent, namely the

'165 application, was filed prior to June 8, 1995. As such, pursuant to 35 U.S.C. 154(c)(1), the term of the '938 patent is the longer of 20 years from the earliest filing date of the domestic priority application, or November 1, 2011, and 17 years from the issue date, or July 30, 2013. Therefore, the expiration date of the '938 patent is July 30, 2013.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 5,540,938 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No terminal disclaimer or certificate of correction has been filed in U.S. Patent No. 5,540,938 ("the '938 patent"). Moreover, the '938 patent has not been reexamined and so no re-examination certificate has been issued in U.S. Patent No. 5,540,938.

The first maintenance fee for the '938 patent was paid on January 28, 2000, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23, 2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

The second maintenance fee for the '938 patent was paid on January 30, 2004, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23,

2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

The third maintenance fee for the '938 patent was paid on January 30, 2008, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23, 2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

Accordingly, there are no unpaid maintenance fees for this patent.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 5,540,938 claims a method of using the Approved Product. At least claims 1, 2, 3 and 8 read on the method of using the Approved Product. These claims are set forth below.

> Claim 1. A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.

Claim 2. A method according to claim 1, wherein the neurological disease is characterised by demyelination of the central nervous system.

Claim 3. A method according to claim 1 or 2, wherein the neurological disease is multiple sclerosis.

Claim 8. A method according to claim 1, wherein the active agent is 4-aminopyridine.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which one claim reads on the method of using the Approved Product is set forth herein below.

CLAIM	The Method Of Using The Approved Product
1. A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.	As shown in the approved labeling (attached as Exhibit 6), AMPYRA is a medicament approved for treatment to improve walking in patients with multiple sclerosis (MS) as demonstrated by an increase in walking speed. MS is a disease characterised by a slowing of nerve impulse transmission. The active ingredient of AMPYRA, dalfampridine, is a mono-aminopyridine. AMPYRA is a controlled release (specifically, an extended release) tablet that is recommended for twice-daily administration and that allows the controlled absorption of dalfampridine and achieves therapeutically effective blood levels over a 12-24 hour period. As noted, AMPYRA is recommended for twice-daily administration.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ('IND") was requested by Rush Presbyterian - St. Luke's Medical Center on November 23, 1979. A copy of this request is provided at Exhibit 9. The FDA assigned IND No. 17,627. Due to transfers of ownership of the IND from Rush Presbyterian - St. Luke's Medical Center to Elan Pharmaceutical Research Corp., from Elan to Athena Neurosciences, Inc., and then from Athena to Acorda Therapeutics, Inc., the acknowledgment letter from FDA of the IND is not presently available to Applicant. However, Applicant believes that the IND became effective by January 1, 1980.

A new drug application ("NDA") was initially submitted on January 30, 2009 and acknowledged as received on this date in a letter from FDA dated February 19, 2009 (Exhibit 10). Following a refusal to file by the FDA, the FDA continued evaluation activities and the Marketing Applicant diligently resubmitted its NDA on April 22, 2009. The NDA number assigned to the application for dalfampridine was 22-250. The NDA was approved on January 22, 2010 (Exhibit 7).

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY OWNER, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of significant activities, undertaken by the Marketing Applicant, its predecessors, and affiliates, in IND No. 17,627 and NDA 22-250 during the applicable regulatory review period with respect of the approved product is provided, respectively, at Exhibits 11 and 12.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (i) the term of the patent has not expired before an application for extension is submitted; (ii) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (iii) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (iv) the product has been subject to a regulatory review period before its commercial marketing or use; and (v) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(i) Pursuant to 35 U.S.C. §154, the term of United States Patent No. 5,540,938 is currently set to expire on July 30, 2013. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 5,540,938.

(ii) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(iii) This application is being submitted by Acorda Therapeutics, Inc., as agent for Applicant, Elan Pharma International Ltd. ("Applicant"), the owner of record of United States Patent No. 5,540,938. (See Exhibit 5). Elan Pharma International Ltd. is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on January 22, 2010, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on March 23, 2010. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(iv) As evidenced by the January 22, 2010 letter from the FDA to Acorda Therapeutics, Inc. (Exhibit 7), the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(v) The permission for the commercial marketing of the AMPYRA™ (dalfampridine) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See, e.g., Section (4), above.)

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 5,540,938, now expiring July 30, 2013, should be extended for 1,826 days, or to July 30, 2018, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 17,627 of January 1, 1980, and the submission of the NDA 22-250 on January 30, 2009 (i.e., the "testing phase"), a period of 10,622 days, plus the length of time between the submission of the NDA 22-250 on January 30, 2009 to

NDA approval on January 22, 2010 (i.e., the "approval phase"), a period of 357 days. These two periods added together equal 10,979 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 10,979 day regulatory review period the following:

(i) 6,055 days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 5,540,938 on July 30, 1996; and

(ii) 2,283 days, which is one-half the number of days remaining in the IND period after the subtraction of 6,055 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 2,640 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (2,283 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (357 days). This length of an extension would provide a new expiration date for U.S. Patent No. 5,540,938 of October 21, 2020. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156. One of these potential limitations does further limit the term of the patent and the other does not.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted (i.e., 1,826 days in this case). Since the current expiry date of U.S. Patent No. 5,540,938 is July 30, 2013, no patent term extension could extend the term of the patent beyond July 30, 2018. Consequently, this provision does operate to limit the possible extension available to U.S. Patent 5,540,938; this leads to a patent term extension period of 1,826 days.

Second, under 35 U.S.C. §156(c)(3), a calculated extension period cannot lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that

is, a patent term expiring after January 22, 2024. In this case, however, 35 U.S.C. §156(c)(3) does not operate to limit the possible extension available to U.S. Patent 5,540,938.

Accordingly, United States Patent No. 5,540,938 is eligible for a patent term extension of 1,826 days.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765).

Elan Pharma International Ltd. ("Applicant') acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In accordance with the duty of disclosure described in 37 C.F.R. § 1.765 and acknowledged under 37 C.F.R. § 1.740(13), Applicant wishes to inform the Office that two patent term extension applications have been filed concurrently with respect to the regulatory review period for AMPYRA™ (dalfampridine) Extended Release Tablets. Such patent term extension applications are with respect to U.S. Patent No. 5,540,938 (i.e., the present application) and U.S. Patent No. 5,370,879. It is requested that the Office examine these applications concurrently so that a meaningful election can be made upon the receipt of a Notice of Final Determination and Requirement of Election as to which patent to ultimately extend in accordance with 37 C.F.R. § 1.785.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Please charge our Deposit Account No. 50-0740 in the amount of $1120.00 to cover the fee for a request for extension of patent term. The Director is hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 029490.00101, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1-12) is attached.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Christopher N. Sipes
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Telephone No.: (202) 662-6000
Facsimile No.: (202) 662-6291

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits 1-12, is accompanied by two additional copies, for a total submission of three copies.

Dated: March 17, 2010

Respectfully submitted,

By _____

Natalie M. Derzko
Registration No.: 48,102
Christopher N. Sipes
Registration No.: 39,837
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000
Attorneys for Acorda Therapeutics, Inc.

Dated: March 17, 2010

Respectfully submitted,

By _____

Michele M. Simkin
Registration No.: 34,717
FOLEY & LARDNER LLP
3000 K Street, N.W.
Washington, DC 20007-5109
(202) 672-5300
Attorney for Elan Pharma International Ltd.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent of:
INVENTOR Masterson, et al.

Patent No.: 5,540,938

Issued: July 30, 1996

For: FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

Mail Stop Patent Ext.
Commissioner for Patents
P.O. Box 1450
Alexandria, VA
22313-1450

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Applicant, Elan Pharma International Ltd., the address of which is Monksland, Athlone Co., Westmeath, Ireland, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,540,938 (Exhibit 1) granted to Joseph G. Masterson and Michael Myers on the 30th day of July, 1996, for "Formulations and their Use in the Treatment of Neurological Diseases" by virtue of an assignment from the inventors to Elan Corporation, PLC, recorded December 17, 1991 at Reel 005960, Frame 0060 (Exhibit 2), and a further assignment from Elan Corporation, PLC to Elan Pharma International Ltd. (Exhibit 3), recorded July 23, 2008 at Reel 021266, Frame 0957. The '938 patent matured from United States Patent Application No. 08/328,165, filed on October 24, 1994 ("the '165 application"). The '165 application is a

divisional of U.S. Patent Application No. 08/073,651, filed on June 7, 1993, now U.S. Patent No. 5,370,879, and a divisional of U.S. Patent Application No. 07/786,400, filed on November 1, 1991, now abandoned.

The approved product that is relevant to this application is AMPYRA™ (dalfampridine) Extended Release Tablets, referred to herein as "AMPYRA" or "Approved Product."

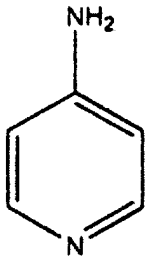
The Marketing Applicant for AMPYRA is Acorda Therapeutics, Inc. A letter on behalf of the Marketing Applicant authorizing the patent owner to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto as Exhibit 4.

The following information is submitted by Acorda Therapeutics, Inc., through its duly authorized attorney, Covington & Burling LLP, on behalf of Applicant (see Exhibit 5), in accordance with 35 U.S.C. §156(d) and the rules for extension of patent term issued by the USPTO at 37 C.F.R. Subpart F, §§1.710 to 1.791 and follows the numerical format set forth in 37 C.F.R. §1.740:

(1) A COMPLETE IDENTIFICATION OF THE APPROVED PRODUCT AS BY APPROPRIATE CHEMICAL AND GENERIC NAME, PHYSICAL STRUCTURE OR CHARACTERISTICS:

The approved product is AMPYRA, an extended release tablet with the active ingredient dalfampridine, available in a 10 mg strength. AMPYRA has been approved as a treatment to improve walking in patients with multiple sclerosis (MS) as demonstrated by an increase in walking speed (approved labeling attached as Exhibit 6). AMPYRA is a potassium channel blocker.

The chemical name of dalfampridine is 4-aminopyridine, with the following chemical structure:



(2) A COMPLETE IDENTIFICATION OF THE FEDERAL STATUTE INCLUDING THE APPLICABLE PROVISION OF LAW UNDER WHICH THE REGULATORY REVIEW OCCURRED:

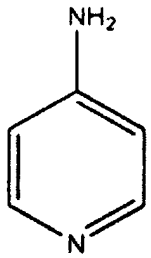
The Approved Product is a drug product that was approved under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 355(b)(1)).

(3) AN IDENTIFICATION OF THE DATE ON WHICH THE PRODUCT RECEIVED PERMISSION FOR COMMERCIAL MARKETING OR USE UNDER THE PROVISION OF LAW UNDER WHICH THE APPLICABLE REGULATORY REVIEW PERIOD OCCURRED:

The Approved Product received permission for commercial marketing or use by the United States Food and Drug Administration (FDA) pursuant to section 505(b)(1) of the FFDCA in a letter dated January 22, 2010. A copy of the approval letter is attached as Exhibit 7.

(4) IN THE CASE OF A DRUG PRODUCT, AN IDENTIFICATION OF EACH ACTIVE INGREDIENT IN THE PRODUCT AND AS TO EACH ACTIVE INGREDIENT, A STATEMENT THAT IT HAS NOT BEEN PREVIOUSLY APPROVED FOR COMMERCIAL MARKETING OR USE UNDER THE FFDCA, THE PUBLIC HEALTH SERVICE ACT, OR THE VIRUS-SERUM-TOXIN ACT OR A STATEMENT OF WHEN THE ACTIVE INGREDIENT WAS APPROVED FOR COMMERCIAL MARKETING OR USE (EITHER ALONE OR IN COMBINATION WITH OTHER ACTIVE INGREDIENTS), THE USE FOR WHICH IT WAS APPROVED, AND THE PROVISION OF LAW UNDER WHICH IT WAS APPROVED: (37 C.F.R. § 1.740(a)(4))

AMPYRA is a potassium channel blocker that has been approved under Section 505(b) of the FFDCA as a treatment to walking in patients with multiple sclerosis (MS). The active ingredient of AMPYRA is dalfampridine (i.e., 4-aminopyridine) with the chemical structure:



Neither dalfampridine, nor any salt or ester of this active ingredient, have been previously approved for commercial marketing or use under the FFDCA, the Public Health Service Act, or the Virus-Serum-Toxin Act. Indeed, the FDA has granted New Chemical Entity (NCE) status to AMPYRA (dalfampridine), indicating that AMPYRA represents the first approval by FDA of a drug product containing the dalfampridine active moiety.

(5) A STATEMENT THAT THE APPLICATION IS BEING SUBMITTED WITHIN THE SIXTY DAY PERIOD PERMITTED FOR SUBMISSION PURSUANT TO SECTION 1.720(f) AND AN IDENTIFICATION OF THE DATE OF THE LAST DAY ON WHICH THE APPLICATION COULD BE SUBMITTED:

This Application is timely filed, pursuant to 35 U.S.C. § 156(d)(1), within the permitted sixty-day (60-day) period that began on January 22, 2010 when the product received permission under 505(b)(1) of the FFDCA and that will expire on March 23, 2010. Applicant understands that, pursuant to 37 C.F.R. § 1.720(f), the USPTO may deem this period to expire one day earlier, on March 22, 2010.

(6) A COMPLETE IDENTIFICATION OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT BY THE NAME OF THE INVENTOR, THE PATENT NUMBER, THE DATE OF ISSUE, AND THE DATE OF EXPIRATION:

UNITED STATES PATENT NO.: 5,540,938

INVENTORS: JOSEPH G. MASTERSON and MICHAEL MYERS

DATE OF ISSUE: JULY 30, 1996

EXPIRATION DATE: JULY 30, 2013

The expiration date of U.S. Patent No. 5,540,938 ("the '938 patent") is July 30, 2013 based on the following information. The patent application that issued as the '938 patent, U.S. Patent Application No. 08/328,165 ("the '165 application), was filed on October 24, 1994, as a divisional of U.S. Patent Application No. 08/073,651, filed on June 7, 1993, now U.S. Patent No. 5,370,879, and a divisional of U.S. Patent Application No. 07/786,400, filed on November 1, 1991, now abandoned. The last filed application that matured into the '938 patent, namely the

'165 application, was filed prior to June 8, 1995. As such, pursuant to 35 U.S.C. 154(c)(1), the term of the '938 patent is the longer of 20 years from the earliest filing date of the domestic priority application, or November 1, 2011, and 17 years from the issue date, or July 30, 2013. Therefore, the expiration date of the '938 patent is July 30, 2013.

(7) A COPY OF THE PATENT FOR WHICH AN EXTENSION IS BEING SOUGHT, INCLUDING THE ENTIRE SPECIFICATION (INCLUDING CLAIMS) AND DRAWINGS:

A complete copy of U.S. Patent No. 5,540,938 is attached as Exhibit 1.

(8) A COPY OF ANY DISCLAIMER, CERTIFICATE OF CORRECTION, RECEIPT OF MAINTENANCE FEE PAYMENT, OR RE-EXAMINATION CERTIFICATE ISSUED IN THE PATENT:

No terminal disclaimer or certificate of correction has been filed in U.S. Patent No. 5,540,938 ("the '938 patent"). Moreover, the '938 patent has not been reexamined and so no re-examination certificate has been issued in U.S. Patent No. 5,540,938.

The first maintenance fee for the '938 patent was paid on January 28, 2000, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23, 2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

The second maintenance fee for the '938 patent was paid on January 30, 2004, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23,

2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

The third maintenance fee for the '938 patent was paid on January 30, 2008, as shown by the attached Patent Bibliographic Sheet obtained from Public PAIR on February 23, 2010 and the USPTO Maintenance Fee Statement for this patent obtained from Public PAIR on March 5, 2010, both found in Exhibit 8.

Accordingly, there are no unpaid maintenance fees for this patent.

(9) A STATEMENT THAT THE PATENT CLAIMS THE APPROVED PRODUCT, OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT, AND A SHOWING WHICH LISTS EACH APPLICABLE PATENT CLAIM AND DEMONSTRATES THE MANNER IN WHICH AT LEAST ONE SUCH PATENT CLAIM READS ON THE APPROVED PRODUCT OR A METHOD OF USING OR MANUFACTURING THE APPROVED PRODUCT:

U.S. Patent No. 5,540,938 claims a method of using the Approved Product. At least claims 1, 2, 3 and 8 read on the method of using the Approved Product. These claims are set forth below.

> Claim 1. A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.

Claim 2. A method according to claim 1, wherein the neurological disease is characterised by demyelination of the central nervous system.

Claim 3. A method according to claim 1 or 2, wherein the neurological disease is multiple sclerosis.

Claim 8. A method according to claim 1, wherein the active agent is 4-aminopyridine.

Pursuant to 37 C.F.R. § 1.740(a)(9), a showing which demonstrates the manner in which one claim reads on the method of using the Approved Product is set forth herein below.

CLAIM	The Method Of Using The Approved Product
1. A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.	As shown in the approved labeling (attached as Exhibit 6), AMPYRA is a medicament approved for treatment to improve walking in patients with multiple sclerosis (MS) as demonstrated by an increase in walking speed. MS is a disease characterised by a slowing of nerve impulse transmission. The active ingredient of AMPYRA, dalfampridine, is a mono-aminopyridine. AMPYRA is a controlled release (specifically, an extended release) tablet that is recommended for twice-daily administration and that allows the controlled absorption of dalfampridine and achieves therapeutically effective blood levels over a 12-24 hour period. As noted, AMPYRA is recommended for twice-daily administration.

(10) A STATEMENT BEGINNING ON A NEW PAGE OF THE RELEVANT DATES AND INFORMATION PURSUANT TO 35 U.S.C. §156(g) IN ORDER TO ENABLE THE SECRETARY OF HEALTH AND HUMAN SERVICES OR THE SECRETARY OF AGRICULTURE, AS APPROPRIATE, TO DETERMINE THE APPLICABLE REGULATORY REVIEW PERIOD AS FOLLOWS:

(i) FOR A PATENT CLAIMING A HUMAN DRUG, ANTIBIOTIC, OR HUMAN BIOLOGICAL PRODUCT, THE EFFECTIVE DATE OF THE INVESTIGATIONAL NEW DRUG APPLICATION (IND) AND THE IND NUMBER; THE DATE ON WHICH A NEW DRUG APPLICATION (NDA) OR A PRODUCT LICENSE APPLICATION (PLA) WAS INITIALLY SUBMITTED AND THE NDA OR PLA NUMBER; AND THE DATE ON WHICH THE NDA WAS APPROVED OR THE PRODUCT LICENSE ISSUED:

An original investigational new drug application ('IND") was requested by Rush Presbyterian - St. Luke's Medical Center on November 23, 1979. A copy of this request is provided at Exhibit 9. The FDA assigned IND No. 17,627. Due to transfers of ownership of the IND from Rush Presbyterian - St. Luke's Medical Center to Elan Pharmaceutical Research Corp., from Elan to Athena Neurosciences, Inc., and then from Athena to Acorda Therapeutics, Inc., the acknowledgment letter from FDA of the IND is not presently available to Applicant. However, Applicant believes that the IND became effective by January 1, 1980.

A new drug application ("NDA") was initially submitted on January 30, 2009 and acknowledged as received on this date in a letter from FDA dated February 19, 2009 (Exhibit 10). Following a refusal to file by the FDA, the FDA continued evaluation activities and the Marketing Applicant diligently resubmitted its NDA on April 22, 2009. The NDA number assigned to the application for dalfampridine was 22-250. The NDA was approved on January 22, 2010 (Exhibit 7).

(11) A BRIEF DESCRIPTION BEGINNING ON A NEW PAGE OF THE SIGNIFICANT ACTIVITIES UNDERTAKEN BY OWNER, THE MARKETING APPLICANT, DURING THE APPLICABLE REGULATORY REVIEW PERIOD WITH RESPECT TO THE APPROVED PRODUCT AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES:

In accordance with 37 C.F.R. § 1.740(a)(11), a list of significant activities, undertaken by the Marketing Applicant, its predecessors, and affiliates, in IND No. 17,627 and NDA 22-250 during the applicable regulatory review period with respect of the approved product is provided, respectively, at Exhibits 11 and 12.

(12) A STATEMENT BEGINNING ON A NEW PAGE THAT IN THE OPINION OF THE APPLICANT THE PATENT IS ELIGIBLE FOR THE EXTENSION AND A STATEMENT AS TO THE LENGTH OF EXTENSION CLAIMED, INCLUDING HOW THE LENGTH OF EXTENSION WAS DETERMINED:

(a) Statement of the eligibility of the patent for extension under 35 U.S.C. §156(a):

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (i) the term of the patent has not expired before an application for extension is submitted; (ii) the term of the patent has never been extended under 35 U.S.C. §156(e)(1); (iii) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d); (iv) the product has been subject to a regulatory review period before its commercial marketing or use; and (v) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product using the provision of law under which such regulatory review period occurred.

As described below by corresponding number, each of these elements is satisfied here:

(i) Pursuant to 35 U.S.C. §154, the term of United States Patent No. 5,540,938 is currently set to expire on July 30, 2013. This application is, therefore, being submitted prior to the expiration of the term of United States Patent No. 5,540,938.

(ii) The term of this patent has never been extended under 35 U.S.C. §156(e)(1).

(iii) This application is being submitted by Acorda Therapeutics, Inc., as agent for Applicant, Elan Pharma International Ltd. ("Applicant"), the owner of record of United States Patent No. 5,540,938. (See Exhibit 5). Elan Pharma International Ltd. is the owner of record by virtue of duly recorded assignments discussed above. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty-day period beginning on January 22, 2010, the date the product received permission for marketing under Section 505 of the FFDCA [21 U.S.C. §355], and ending on March 23, 2010. Moreover, this application contains the information required under 35 U.S.C. §156(d).

(iv) As evidenced by the January 22, 2010 letter from the FDA to Acorda Therapeutics, Inc. (Exhibit 7), the product was subject to a regulatory review period under Section 505(b) of the FFDCA before its commercial marketing or use.

(v) The permission for the commercial marketing of the AMPYRA™ (dalfampridine) product is the first permitted commercial marketing and use under Section 505 of the FFDCA [21 U.S.C. §355] of the product, as defined in 35 U.S.C. § 156(f). (See, e.g., Section (4), above.)

(b) Statement as to length of extension claimed.

The term of U.S. Patent No. 5,540,938, now expiring July 30, 2013, should be extended for 1,826 days, or to July 30, 2018, in accordance with 35 U.S.C. §156.

As set forth in 35 U.S.C. §156(g)(1), the regulatory review period equals the length of time between the effective date of IND No. 17,627 of January 1, 1980, and the submission of the NDA 22-250 on January 30, 2009 (i.e., the "testing phase"), a period of 10,622 days, plus the length of time between the submission of the NDA 22-250 on January 30, 2009 to

NDA approval on January 22, 2010 (i.e., the "approval phase"), a period of 357 days. These two periods added together equal 10,979 days.

Pursuant to 37 C.F.R. § 1.775(d), the term of the patent as extended is determined by subtracting from the 10,979 day regulatory review period the following:

(i) 6,055 days, which is the number of days in the IND and NDA periods on or before the issuance of U.S. Patent No. 5,540,938 on July 30, 1996; and

(ii) 2,283 days, which is one-half the number of days remaining in the IND period after the subtraction of 6,055 days above (wherein half days are ignored for purposes of this subtraction, as provided by 37 C.F.R. § 1.775(d)(1)(iii)).

From the foregoing calculation, an extension of 2,640 days results, i.e., the remaining period under 35 U.S.C. 156(g)(1)(B)(i) (2,283 days) plus the remaining period under 35 U.S.C. §156(g)(1)(B)(ii) (357 days). This length of an extension would provide a new expiration date for U.S. Patent No. 5,540,938 of October 21, 2020. However, this extension period is subject to two further potential limitations under 35 U.S.C. §156. One of these potential limitations does further limit the term of the patent and the other does not.

First, under 35 U.S.C. §156(g)(6)(A), a maximum extension of five years is permitted (i.e., 1,826 days in this case). Since the current expiry date of U.S. Patent No. 5,540,938 is July 30, 2013, no patent term extension could extend the term of the patent beyond July 30, 2018. Consequently, this provision does operate to limit the possible extension available to U.S. Patent 5,540,938; this leads to a patent term extension period of 1,826 days.

Second, under 35 U.S.C. §156(c)(3), a calculated extension period cannot lead to a patent term that would result in a patent term exceeding 14 years after the date of approval, that

is, a patent term expiring after January 22, 2024. In this case, however, 35 U.S.C. §156(c)(3) does not operate to limit the possible extension available to U.S. Patent 5,540,938.

Accordingly, United States Patent No. 5,540,938 is eligible for a patent term extension of 1,826 days.

(13) A STATEMENT THAT APPLICANT ACKNOWLEDGES A DUTY TO DISCLOSE TO THE COMMISSIONER OF PATENTS AND TRADEMARKS AND THE SECRETARY OF HEALTH AND HUMAN SERVICES ANY INFORMATION WHICH IS MATERIAL TO THE DETERMINATION OF ENTITLEMENT TO THE EXTENSION SOUGHT (SEE 37 C.F.R. §1.765).

Elan Pharma International Ltd. ("Applicant') acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In accordance with the duty of disclosure described in 37 C.F.R. § 1.765 and acknowledged under 37 C.F.R. § 1.740(13), Applicant wishes to inform the Office that two patent term extension applications have been filed concurrently with respect to the regulatory review period for AMPYRA™ (dalfampridine) Extended Release Tablets. Such patent term extension applications are with respect to U.S. Patent No. 5,540,938 (i.e., the present application) and U.S. Patent No. 5,370,879. It is requested that the Office examine these applications concurrently so that a meaningful election can be made upon the receipt of a Notice of Final Determination and Requirement of Election as to which patent to ultimately extend in accordance with 37 C.F.R. § 1.785.

(14) THE PRESCRIBED FEE FOR RECEIVING AND ACTING UPON THE APPLICATION FOR EXTENSION (SEE 37 C.F.R. §1.20(j)):

Please charge our Deposit Account No. 50-0740 in the amount of $1120.00 to cover the fee for a request for extension of patent term. The Director is hereby authorized to charge our Deposit Account No. 50-0740, under Docket No. 029490.00101, for any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm), to prevent this application from being inadvertently abandoned. A duplicate of this Request (without Exhibits 1-12) is attached.

(15) THE NAME, ADDRESS, AND TELEPHONE NUMBER OF THE PERSON TO WHOM INQUIRIES AND CORRESPONDENCE RELATING TO THE APPLICATION FOR PATENT TERM EXTENSION ARE TO BE DIRECTED:

Christopher N. Sipes
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Telephone No.: (202) 662-6000
Facsimile No.: (202) 662-6291

Pursuant to 37 C.F.R. §1.740(b), this Request for Extension of Patent Term Under 35 U.S.C. §156, including Exhibits 1-12, is accompanied by two additional copies, for a total submission of three copies.

Dated: March 17, 2010

Respectfully submitted,

By_____

Natalie M. Derzko
Registration No.: 48,102
Christopher N. Sipes
Registration No.: 39,837
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
(202) 662-6000
Attorneys for Acorda Therapeutics, Inc.

Dated: March 17, 2010

Respectfully submitted,

By_____

Michele M. Simkin
Registration No.: 34,717
FOLEY & LARDNER LLP
3000 K Street, N.W.
Washington, DC 20007-5109
(202) 672-5300
Attorney for Elan Pharma International Ltd.

US005540938A

United States Patent [19]

Masterson et al.

[11] Patent Number: 5,540,938

[45] Date of Patent: Jul. 30, 1996

Exhibit 1

[54] **FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES**

[75] Inventors: **Joseph G. Masterson**, London, United Kingdom; **Michael Myers**, Athlone, Ireland

[73] Assignee: **Elan Corporation, plc**, Athlone, Ireland

[21] Appl. No.: **328,165**

[22] Filed: **Oct. 24, 1994**

Related U.S. Application Data

[62] Division of Ser. No. 786,400, Nov. 1, 1991, abandoned, and a division of Ser. No. 73,651, Jun. 7, 1993, Pat. No. 5,370,879.

[51] **Int. Cl.**[6] **A61K 9/16**; A61K 9/50; A61K 9/62; A61K 9/70

[52] **U.S. Cl.** **424/490**; 424/445; 424/449; 424/451; 424/452; 424/458; 424/460; 424/461; 424/464; 424/465; 424/474; 424/475; 424/480; 424/484; 424/489; 424/494; 424/495; 424/497; 424/498; 424/499

[58] **Field of Search** 424/445, 449, 424/451, 452, 458, 460, 461, 464, 465, 474, 475, 480, 484, 489, 494, 495, 497, 498, 499

[56] **References Cited**

PUBLICATIONS

Davis et al., "D. of the Rush Multiple Sclerosis Center".

Bever et al., Ann. Neurol. 27(4), pp. 421–427 (Apr. 1990).

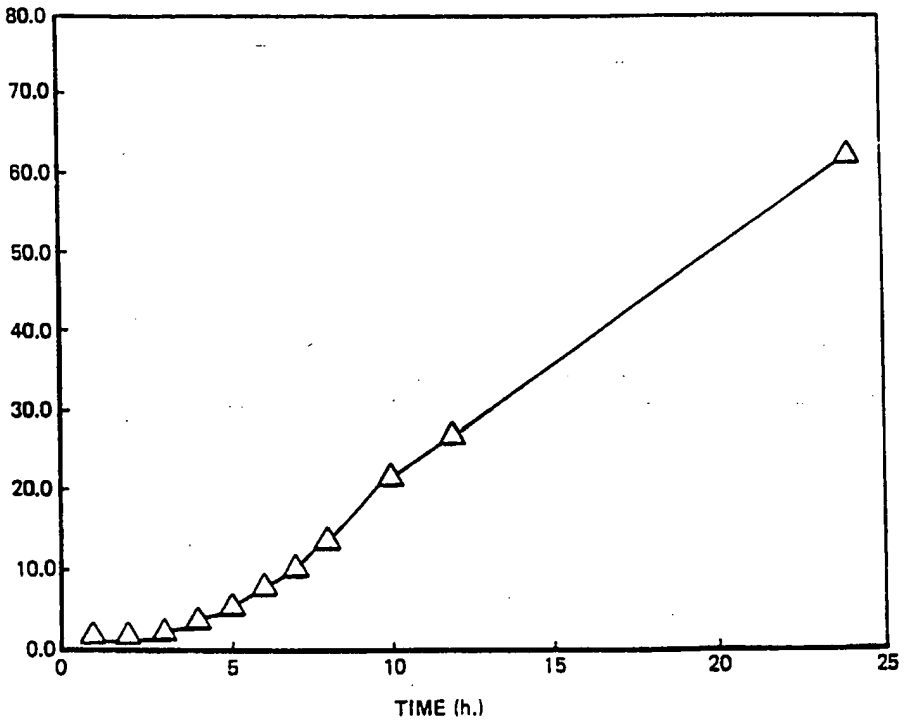
Wesseling et al., N. Eng. J. of Med., 310(15), pp. 988–989 (Apr. 1984).

Primary Examiner—Thurman Page
Assistant Examiner—Carlos Azpuru
Attorney, Agent, or Firm—Marla J. Church

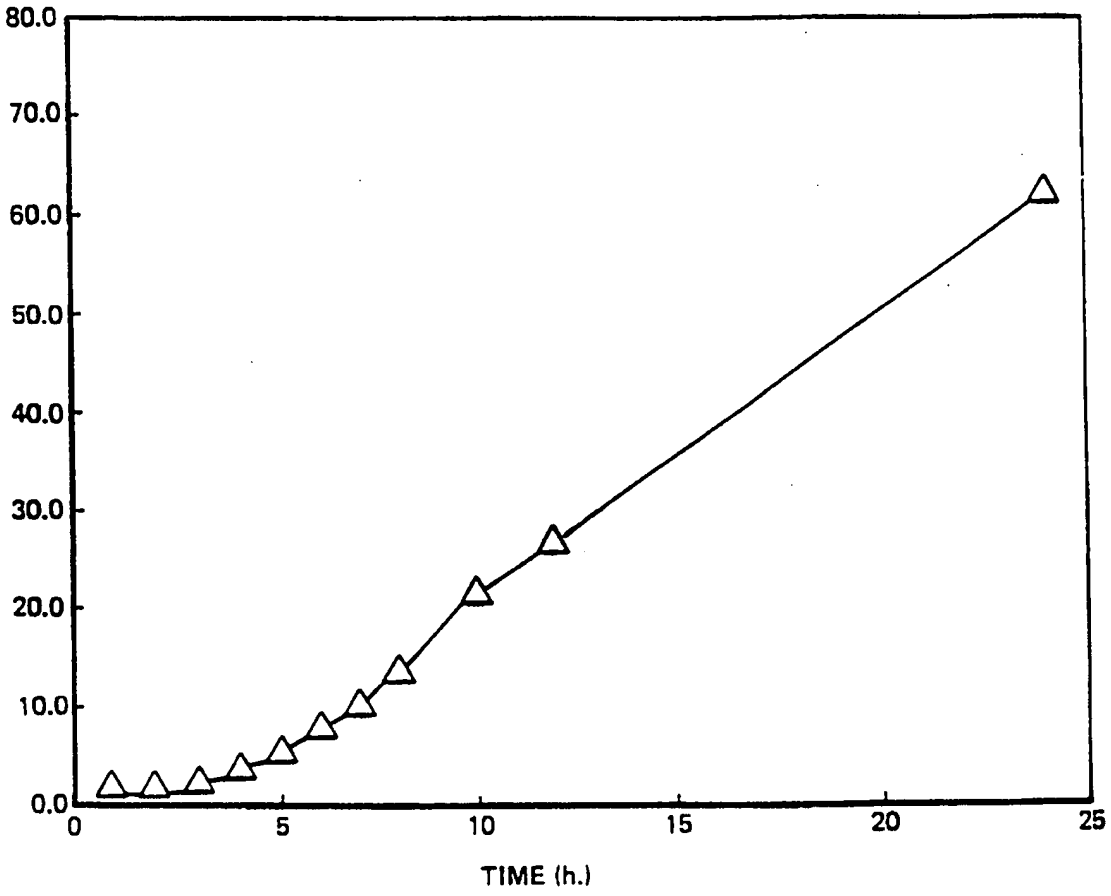
[57] **ABSTRACT**

Pharmaceutical formulations comprise a mono- or di-aminopyridine active agent for administration on a once- or twice-daily basis for use in the treatment of neurological diseases, in particular multiple sclerosis and Alzheimer's disease. The formulations, which are suitable for oral or percutaneous administration of the active agent, include the active agent in a carrier effective to permit release of the mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12–24 hours following administration.

8 Claims, 1 Drawing Sheet



4—AP % RELEASE



4—AP % RELEASE

FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

This is a divisional Ser. No. 07/786,400 filed on Nov. 1, 1991now abandoned, and Ser. No. 08,073,651 filed Jun. 7, 1993, now U.S. Pat. No. 5,370,879.

FIELD OF THE INVENTION

This invention relates to preparations for use in the treatment of neurological diseases. More particularly, the invention relates to preparations for the controlled administration of mono- or diaminopyridine active agents and to the use of such preparations in the treatment of neurological diseases characterised by a slowing of nerve impulse transmission, more especially multiple sclerosis and Alzheimer's disease.

BACKGROUND AND PRIOR ART

Multiple sclerosis (MS) is a degenerative and inflammatory neurological disease which affects the central nervous system, more specifically the myelin sheath. MS causes demyelination of nerve fibres resulting in short-circuiting of nerve impulses and thus a slowing or blocking of transmission along the nerve fibres, with associated disabling symptoms.

Alzheimer's disease is a major cause of dementia in the elderly. It may be described as a progressive pathological deterioration in personality, memory and intellect consistent with a generalised atrophy of corresponding brain centres. The emotional state, behaviour, cognitive function and thought processes of sufferers are all adversely affected. A minor disimprovement in memory which gradually becomes more apparent is the first indication of the onset of the disease.

The incidence of the condition is slightly less than 1% of the general population of the U.K. but rises to 5% in the over-65's and to 20% in the over-80's.

The biochemical basis and neuropathology of the disease are better understood than its aetiology. The possibility of a genetic link is being investigated, as are suggestions that aluminium is a causative factor.

Treatments available to date are of, at best, limited value and the progression of the disease is irreversible. Death normally occurs less than a decade after the illness first presents itself (Barker, S. and Branford, D.;Pharm. Journal Jan. 26, 1991, pp 116–118).

4-Aminopyridine (4-AP) has been found to improve the conduction of nerve impulses, thereby, alleviating symptoms in MS patients. 4-AP has been found to slow the potassium ion flow in nerve impulse transmission and, thereby, is effective in restoring conduction in blocked demyelinated nerves. In clinical trials carried out by Davis, F. A. and Stefoski, D. of The Rush Multiple Sclerosis Centre, U.S.A., 4-AP has been administered orally in multiple daily doses over 2–5 days to MS patients with mild to marked improvements being noted and minimal side effects.

3,4-Di-aminopyridine (3,4-DAP) has also been found to improve specific neurological deficits and visual evoked response latencies in MS patients when administered orally in multiple daily doses. Bever, C. T. JR; Leslie, J.; Camenga, D. L.; Panitch, H. S.; and Johnson, K. P., Ann. Neurol. 27(4), pp. 421–427 (Apr. 1990).

4-AP has also been found to improve the mental functions in patients with Alzheimer's disease. This effect is believed to be related to the potassium channel blocking action of 4-AP which in turn enhances calcium influx into the neuron thus prolonging nerve action potential and increasing transmitter release. Wesseling et at., N. Eng. J. of Med. 310 (15), pp. 988–989 (Apr. 1984).

In the use of a drag for long-term therapy it is desirable that the drug be formulated so that it is suitable for once- or twice-daily administration to aid patient compliance. Further, in view of the nature of neurological diseases, it can be appreciated that there is a need for an improved dosage form. However, such a formulation must result in a controlled release of drug to the systemic circulation and therapeutically effective blood levels throughout a given treatment period.

Another problem with long-term therapy is the requirement of determining an optimum dose which can be tolerated by the patient. If such a dose is not determined this can lead to a diminution in the effectiveness of the drag being administered.

It is an object of the present invention to provide preparations suitable for the long-term administration of a mono- or di-aminopyridine active agent.

It is a further object of the present invention to provide the use of a mono- or di-aminopyridine active agent in a manner which enables one to achieve a tolerable state for said drag in a subject being treated therewith.

SUMMARY OF THE INVENTION

According to the invention there is provided a pharmaceutical formulation comprising a mono- or di-aminopyridine for administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12–24 hours following administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of release of 4-AP (%) versus time (hours) for a patch as prepared in Example 11.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The pharmaceutical formulations according to the invention include pharmaceutical formulations for oral administration and pharmaceutical formulations for administration by the percutaneous route.

According to one aspect of the invention them is provided a pharmaceutical formulation which comprises a pellet for oral administration, said pellet comprising a core of a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 10:1 to 1:20, and a multilayer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said mem-

brane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said mono- or di-aminopyridine from said pellet at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period following oral administration, said rate being measured in vitro as a dissolution rate of said pellet, which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following:

a) no more than 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) no more than 75% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus; and

c) 100% of the mono- or di-aminopyridine is released no earlier than after 8 hours of measurement in said apparatus.

Thus the pharmaceutical formulations according to the invention for oral administration can be administered on a once- or twice-daily basis.

Preferred pharmaceutical formulations according to the invention for oral administration are in a multi-particulate form, from which the active agent is released at a rate to maintain therapeutically effective blood levels over a 12 hour period or a 24 hour period, as required.

According to one embodiment, the release of active agent from the pellet is at a rate allowing controlled absorption thereof over a 24 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

The formulation for once-daily administration can include an amount of a rapid release form of the active agent as hereinafter described, so as to obtain a relatively immediate therapeutic response.

Pharmaceutical formulations according to the invention for once-daily administration can maintain therapeutically effective blood levels substantially over 24 hours with peak plasma levels occurring between 2 and 16 hours, more especially between 4 and 10 hours.

The desired time to peak plasma level is defined as the Tmax of the formulation.

According to a second embodiment, the release of active agent from the pellet is at a rate allowing controlled absorption thereof over a 12 hour period following oral administration, said rate being measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. which substantially corresponds to the following dissolution pattern:

a) from 0 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 20 to 60% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 30 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total is released after 12 hours of measurement in said apparatus.

The formulation for twice-daily administration can also include an amount of a rapid release form of the active agent as hereinafter described, so as to obtain a relatively immediate therapeutic response.

Pharmaceutical formulations according to the invention for twice-daily administration can maintain therapeutically effective blood levels substantially over 12 hours with peak plasma levels occurring between 1 and 10 hours, more especially between 2 and 8 hours.

The core of the pellet formulations according to the invention preferably comprises:

a) a powder mixture containing a mono- or di-aminopyridine or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient, and

b) a polymeric material containing a major proportion of a pharmaceutically acceptable water soluble polymer and a minor proportion of a pharmaceutically acceptable water insoluble polymer,

said core comprising layers of said powder mixture and said polymeric material superimposed one upon the other and said polymeric material being present in an amount effective to ensure that all of said powder mixture is coated into said core.

The term water soluble polymer as used herein includes polymers which are freely permeable to water, whilst the term water insoluble polymer as used herein includes polymers which are slightly permeable to water, as hereinafter indicated.

Preferably the water soluble polymer in the core or membrane is the same or different and is selected from polyvinyl alcohol, polyvinylpyrrolidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, agar, carrageenan, xanthan or polyethylene glycol or a mixture thereof.

Alternatively, the water soluble polymer in the core or membrane can be replaced by a polymeric material which is freely permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

A suitable polymer which is freely permeable to mono- or di-aminopyridine and water is a polymer sold under the Trade Mark EUDRAGIT RL.

Preferably, the water insoluble polymer in the core or membrane is selected from ethylcellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, cellulose triacetate, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene oxide), poly(ethylene terephtalate), poly(vinyl

isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) or polyurethane or a mixture thereof.

The water insoluble polymer of the core or membrane may also comprise naturally occurring polymers or resins.

Thus other preferred water insoluble polymers are selected from a naturally occurring polymer selected from shellac, chitosan, gum juniper or a mixture thereof.

Alternatively, the water insoluble polymer in the core or membrane can be replaced by a polymeric material which is slightly permeable to mono- or di-aminopyridine and water and comprises a copolymer of acrylic and methacrylic acid esters.

A suitable polymer which is slightly permeable to mono- or di-aminopyridine and water is a polymer sold under the Trade Mark EUDRAGIT RS or a polymer whose permeability is pH dependent and sold under the Trade Mark EUDRAGIT L, EUDRAGIT S or EUDRAGIT E. Especially preferred polymers in this category are EUDRAGIT S.

EUDRAGIT polymers are polymeric lacquer substances based on acrylates and/or methacrylates. The polymeric materials sold under the Trade Mark EUDRAGIT RL and EUDRAGIT RS are acrylic resins comprising copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups and are described in the "EUDRAGIT" brochure of Messrs. Rohm Pharma GmbH (1984) wherein derailed physical-chemical data of these products is given. The ammonium groups am present as salts and give rise to the permeability of the lacquer films. EUDRAGIT RL and RS are freely permeable (RL) or slightly permeable (RS), respectively, independent of pH.

EUDRAGIT S is an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester. It is insoluble in acids and pure water. It becomes soluble in a neutral to weakly alkaline milieu by forming salts with alkalis. The permeability of EUDRAGIT S is pH dependent. Above pH 6.0 the polymer becomes increasingly permeable. EUDRAGIT S is described in the "EUDRAGIT S" brochure of Messrs. Rohm Pharma GmbH (1986) wherein detailed physical-chemical data of the product is given.

The core suitably has a number of layers of the core-forming materials and is built up in a manner known per se.

The active agent, pharmaceutically acceptable excipient(s) and the polymeric material can be built up on an inert core. The inert core is preferably a non-pareil seed of sugar/starch having an average diameter in the range 0.2–1.4 mm, more especially, 0.3–0.8 mm.

The mono- or di-aminopyridine and pharmaceutically acceptable excipient(s) are blended to form a homogeneous powder. The mono- or di-aminopyridine component and pharmaceutically acceptable excipient(s) are preferably present in a ratio of from 4:1 to 1:5, more especially 1:3 to 1:1.

The blend is suitably passed through an appropriate mesh screen using a milling machine. In the case of coating in a conventional coating pan, alternate layers of a coating solution/suspension of the polymeric material and the powder are applied to the central inert core to build up the multi-layer arrangement of the core. In the case of an automatic coating system, the coating solution/suspension of the polymeric material and the powder are applied, simultaneously, in conventional manner.

The coating solution/suspension of the polymeric material comprises one or more polymer(s) dissolved/suspended in a suitable solvent or mixture of solvents. The concentration of the polymeric material in the coating solution/suspension is determined by the viscosity of the final solution/suspension. Preferably, between 5 and 50 parts of the central inert cores are used relative to the homogeneous powder. The addition of a plasticizing agent to the polymeric solution/suspension may be necessary depending on the formulation to improve the elasticity and also the stability of the polymer film and to prevent changes in the polymer permeability over prolonged storage.

Such changes could affect the drug release rate. Suitable plasticizing agents include polyethylene glycol, propylene glycol, glycerol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and varying percentages of acetylated monoglycerides.

Alternatively, the active agent, pharmaceutically acceptable excipient(s) and polymeric material can be built up on a central active core. The active core is suitably formed by blending the mono- or diaminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder, shaping a portion of said blend to form a central core and applying the remainder of said blend alternately or simultaneously with a polymer binding solution to form a layered structure on said central core.

The completed active cores preferably have an average diameter in the range 0.4–1.6 mm, more especially, 0.6–1.2 mm.

The active core is formed by blending mono- or di-aminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder. A portion of the blend is shaped to form a central core. A multi-layer arrangement is then built up by a successive layering and binding process wherein the remainder of the blend and a polymer binding solution are applied to the active core in alternate layers in a conventional coating pan. Alternatively, an automatic coating system may be used wherein the remainder of the blend and polymer binding solution is applied to the active core, simultaneously. Conventional automated coating systems include for example a CF granulator or a Glatt fluidized bed. The cores are formed to assure a uniform distribution of mono- or di-aminopyridine and excipient ingredients throughout the cores.

As indicated above, the pellet formulations for oral administration in accordance with the invention can include an amount of a rapid release form of active agent so as to obtain a relatively immediate therapeutic response, together with the prolonged effects hereinabove described.

Thus according to a third embodiment of the invention there is provided a controlled absorption mono- or di-aminopyridine formulation for oral administration, comprising pellets as hereinbefore defined and including a sufficient quantity of a rapid release form of mono- or di-aminopyridine to ensure prompt achievement of therapeutically effective blood levels together with therapeutically effective blood levels over a 12 to 24 hour period following each oral administration.

A preferred such controlled absorption formulation in accordance with the invention has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 60% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 50 to 90% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus.

A preferred controlled absorption formulation in accordance with the invention for once-daily administration has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 10 to 40% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 25 to 65% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus;

d) from 50 to 90% of the total mono- or di-aminopyridine is released after 12 hours of measurement in said apparatus; and

e) not less than 75% of the total mono- or di-aminopyridine is released after 24 hours of measurement in said apparatus.

A preferred controlled absorption formulation in accordance with the invention for twice-daily administration has a dissolution rate which when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia XXII in water and at 50 r.p.m. substantially corresponds to the following dissolution pattern:

a) from 20 to 50% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus;

b) from 30 to 70% of the total mono- or di-aminopyridine is released after 4 hours of measurement in said apparatus;

c) from 40 to 80% of the total mono- or di-aminopyridine is released after 8 hours of measurement in said apparatus; and

d) not less than 75% of the total mono- or di-aminopyridine is released after 12 hours in said apparatus.

The controlled absorption formulation according to the invention can comprise a blend of pellets as hereinbefore defined, together with up to 60% by weight of said rapid release form of mono- or diaminopyridine, more especially 10–40% by weight in the case of a once-daily formulation and 20–50% by weight in the case of a twice-daily formulation.

The rapid release form of the active agent can comprise rapid release pellets or granulates.

Preferably, the rapid release pellets comprise a core of mono- or di-aminopyridine active agent or a pharmaceutically acceptable salt thereof in association with one or more pharmaceutically acceptable excipient(s), the mono- or di-aminopyridine component and the pharmaceutically acceptable excipient(s) being present in a ratio of from 0:1 to 1:20 and a multi-layer membrane surrounding said core and containing a major proportion of a pharmaceutically acceptable film-forming, water soluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water insoluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer being effective to allow relatively immediate release of the active agent from said pellet.

Further, preferably, the pellets have a dissolution rate, which when measured in vitro in a type II dissolution apparatus according to US Pharmacopoeia XXII in water at 50 r.p.m. substantially corresponds to the following dissolution pattern:

(a) not less than 70% of the total mono- or di-aminopyridine is released after 1 hour of measurement in said apparatus; and

(b) not less than 85% of the total mono- or di-aminopyridine is released after 2 hours of measurement in said apparatus.

Depending on the function of the pellets, the polymeric material of the core or membrane will consist solely of a water insoluble polymer or a polymer which is slightly permeable to water and aqueous solutions of mono- or di-aminopyridine. However, the polymeric material of the core or membrane may also consist solely of a water soluble polymer or a polymer which is freely permeable to aqueous solutions of mono- or di-aminopyridine in water, especially in the case of the rapid release pellets.

The polymeric material of the core preferably consists solely of a water insoluble polymer or a polymer which is slightly permeable to water and aqueous solutions of mono- or di-aminopyridine. Alternatively, the polymeric material of the core may consist solely of a water soluble polymer or a polymer which is freely permeable to aqueous solutions of mono- or di-aminopyridine and water as indicated above. The polymeric material of the core may include a combination of a water insoluble polymer with a water soluble polymer. The ratio of water soluble/freely permeable to water insoluble/slightly permeable polymer is determined by the particular combination of polymers selected.

The term pharmaceutically acceptable excipient is used herein to define material(s) which is/are homogeneously mixed with the mono- or di-aminopyridine to form the pellet. These materials may also include ingredients known to act as lubricants. Representative excipients include: microcrystalline cellulose (such as that sold under the Trade Mark AVICEL); colloidal silicon dioxide (such as that sold under the Trade Mark AEROSIL); lactose; talc; starch; sorbitol; and cyclodextrin. These may be used singly or in combination with each other. Especially preferred excipients are talc and lactose.

Preferred coating materials include-solutions/suspensions of the polymers cited for use in the application of the powder blend to the central cores in a suitable organic/aqueous carrier medium.

The membrane of the film-forming polymer or mixture of polymers surrounding the core preferably has a proportion of a polymer which is slightly permeable to mono- or di-aminopyridine and water and optionally a proportion of a water permeable polymer, the ratio of water slightly permeable to water permeable polymer being determined by the inherent permeability characteristics of the polymer(s) selected.

As indicated above, the membrane may also be composed of a proportion of a polymer which is water insoluble and a proportion of a polymer which is water soluble, the ratio of water insoluble to water soluble polymer being determined by the inherent permeability characteristics of the respective polymers.

Normally the ratio of water insoluble/slightly permeable polymers to water soluble/permeable polymers lies between 1:5 and 50:1, more especially 1:2 and 20:1. Examples of each of these types of polymer are described above. Especially suitable water soluble/permeable polymers include polyvinylpyrrolidone, polyvinyl alcohol and EUDRAGIT RL, whilst suitable water insoluble/slightly permeable polymers include ethyl cellulose, cellulose acetate, EUDRAGIT

RS, EUDRAGIT L, EUDRAGIT E and EUDRAGIT S. Commercially available ready-made polymeric solutions/suspensions may also be used. These ready-made solutions/suspensions may optionally contain plasticizing agents to improve the polymer film as hereinbefore described. Examples of ready-made solutions/suspensions of polymeric material with or without plasticizing agent include EUDRAGIT RL 30D, EUDRAGIT NE 30D, EUDRAGIT E 12.5, EUDRAGIT L 12.5 P, EUDRAGIT E 12.5, EUDRAGIT S 12.5 P, EUDRAGIT RL 12.5, EUDRAGIT RS 300, EUDRAGIT RS 12.5, AQUACOAT (a Trade Mark of FMC Corporation) and SURE-LEASE (a Trade Mark of Colorcon Inc.).

The water insoluble polymer of the membrane may also comprise naturally occurring polymers or resins. Especially suitable water insoluble, naturally occurring polymers include shellac, chitosan, gum juniper or a mixture thereof.

The membrane may be built up by applying a plurality of coats of membrane polymer solution or suspension to the core as hereinafter described. The membrane solution or suspension contains the polymer(s) dissolved or suspended, respectively, in a suitable aqueous or organic solvent or mixture of solvents, optionally in the presence of a lubricant. Suitable lubricants are talc, stearic acid, magnesium stearate and sodium stearate. A particularly preferred lubricant is talc. The membrane, polymer or mixture of polymers may optionally include a plasticizing agent, the function and choice of which has been previously described.

The dissolution rate achieved is proportionally slower as the amount of membrane applied is increased.

The membrane solution or suspension may be applied to the active cores in a conventional coating pan as indicated or, alternatively, using an automated system such as a CF granulator, for example, a FREUND CF granulator, a GLATT fluidised bed processor, an AEROMATIC, a modified ACCELA-COTA or any other suitably automated bead coating equipment (FREUND, GLATT, AEROMATIC and ACCELA-COTA are all Trade Marks).

Preferably 2–75 ml of membrane solution/suspension is applied per application per kilogram of cores. In an automated system the total amount of membrane solution/suspension applied to the cores is the same as that applied in a conventional coating pan, except that the membrane solution/suspension may be applied continuously.

Preferably, when a coating pan is used the membrane is applied at a rate of 5–30 applications/day until all of the applications have been applied. Between days the pellets are dried for a suitable period of time at a controlled temperature.

The type II dissolution apparatus referred to above is a paddle-type apparatus for carrying out method II according to U.S. Pharmacopoeia XXII.

The pellets or granulates may be compressed into tablets using a binder and/or hardening agent commonly employed in tabletting such as microcrystalline cellulose sold under the Trade Mark "AVICEL" or a co-crystallised powder of highly modified dextrins (3% by weight) and sucrose sold under the Trade Mark "DI-PAC" in such a way that the specific dissolution rate of the pellets is maintained.

Pellets or a combination of pellets in accordance with the invention may also be filled into hard or soft gelatine capsules.

The mono- or di-aminopyridine active agent can form quaternary ammonium-type salts. However, given the solubility of mono- or di-aminopyridines, the formation of pharmaceutically acceptable salts would not normally be required.

According to a further aspect of the invention there is provided a preparation for the once-daily, percutaneous administration of a mono- or di-aminopyridine active agent, which formulation comprises said mono- or di-aminopyridine uniformly distributed in a solid, semi-solid or mucilaginous medium which can be placed in intimate contact with the skin, the release of said mono- or di-aminopyridine from said formulation being at a rate sufficient to achieve therapeutically effective blood levels over a period of 12 to 24 hours following topical application of said preparation.

The invention also provides a preparation for the once-daily, percutaneous administration of a mono- or di-aminopyridine active agent, which formulation comprises said mono- or di-aminopyridine uniformly distributed in a solid, semi-solid or mucilaginous medium which can be placed in intimate contact with the skin, the release of said mono- or di-aminopyridine from said formulation being at a rate allowing controlled absorption thereof over a 24 hour period following topical application of said preparation, said rate being measured in vivo and having a Tmax between 2 and 16 hours.

The formulation for percutaneous administration preferably contains 10–100mg of active agent, more especially 25–75mg of active agent.

The term solidifying agent as used herein also embraces thickening, hardening, setting, suspending or like agents.

Suitable materials for use as the solidifying or gel-forming agent in the preparations according to the invention include, for example, plant extracts, vegetable oils, gums, synthetic or natural polysaccharides, polypeptides, alginates, hydrocarbons, synthetic polymers, minerals and silicon compounds and mixtures thereof.

Suitable plant extracts include agar, ispaghula, psyllium, cydonia and ceratonia or a mixture thereof.

A suitable vegetable oil is hydrogenated castor oil.

Examples of suitable gums include guar gum, acacia gum, ghatti gum, karaya gum, tragacanth gum and xanthan gum or a mixture thereof. Such gums are especially suited for use in accordance with the invention.

Suitable synthetic and natural polysaccharides include alkylcelluloses, hydroxalkylcelluloses, cellulose ethers, cellulose esters, nitrocelluloses, dextrin, agar, carrageenan, pectin, furcellaran and starch or starch derivatives and mixtures thereof. An example of a preferred starch derivative is sodium starch glycolate. Especially preferred polysaccharides include agar and carrageenan.

Suitable polypeptides include zein, gelatin, collagen or polygeline or a mixture thereof.

Suitable alginates include alginic acid, propylene glycol alginate or sodium alginate or a mixture thereof.

Preferred hydrocarbons include soft paraffin and hard paraffin, especially white petrolatum.

An especially preferred synthetic polymer is a carboxyvinyl polymer sold under the Trade Mark CARBOMER.

Suitable minerals include bentonite, hectorite, aluminum magnesium silicate and magnesium silicate or a mixture thereof.

Suitable compounds based on silicon include colloidal silicon dioxide, silicones, polysiloxanes and silica gels or a mixture thereof.

The term "agar" as used herein is synonymous with "agar-agar".

The formulation for percutaneous administration is preferably formed by adding a given amount of the active agent to a solution of a solidifying or gel-forming agent or a mixture thereof in a suitable solvent or mixture of solvents and mixing or heating the mixture thereby obtained so as to form said solid, semi-solid or mucilaginous medium.

The solvent used is preferably water. However, the solvent used may also suitably be an alcohol such as ethanol or stearyl alcohol, glycerol, propylene glycol, polyethlene glycol or a silicone or a mixture thereof, including a mixture with water.

The formulation for percutaneous administration when in the form of a solid or semi-solid preferably has a surface area in the range 2 to 15 cm^2, more especially 5 to 10 cm^2.

The thickness of the formulation for percutaneous administration is preferably in the range 0.5 to 3 mm, more especially in the range 1 to 2mm.

The formulation for percutaneous administration according to the invention may also include one or more auxilary agent(s) selected from an antimicrobial agent, a preservative, an antioxidant, a pH-controlling agent, a plasticizer, a surfactant, a penetration enhancer, a humectant, a local anaesthetic, an anti-irritant agent or a rubefacient or a mixture thereof.

Suitable antimicrobial agents/preservatives include benzalkonium chloride, cetrimide (cetyltrimethylammonium bromide), benzoic acid, benzyl alcohol, Parabens (Trade Mark for the methyl-, ethyl-, propyl- and butyl-esters of para-hydroxybenzoic acid) chlorhexidine, chlorobutanol, phenylmercuric acetate, borate and nitrate, potassium sorbate, sodium benzoate, sorbic acid and thiomersal (mercurithiosalicylate) or a mixture thereof.

Preferred antioxidants, when used in the formulations for percutaneous administration according to the invention, include sodium metabisulphite, sodium sulphite, butylated hydroxyanisole and butylated hydroxytoluene or a mixture thereof.

Preferred pH-controlling agents, when used in the formulations for percutaneous administration according to the invention, include citric acid and sodium citrate.

Preferred plasticizers, when used in the formulations for percutaneous administration according to the invention, include diethylphthalate, dibutylphthalate and tributylcitrate or a mixture thereof.

Suitable surfactants, when used in the formulations for percutaneous administration according to the invention, include sodium lauryl sulphate, diethylene glycol monostearate, propylene glycol monostearate, polyethylene glycols as sold under the Trade Mark MACROGOL, polysorbates and polyvinyl alcohol or a mixture thereof.

Suitable penetration enhancers, when used in the formulations for percutaneous administration according to the invention, include dimethylsulphoxide, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone, N-methyl-2-pyrrolidone and 1-dodecyl azacyclo-heptan-2-one or a mixture thereof.

A particularly preferred humectant, when used in the formulations for percutaneous administration according to the invention, is glycerol. As indicated above glycerol may also be used as a solvent in forming the formulations for percutaneous administration according to the invention and when used as such will confer humectant properties on said formulation.

Suitable local anaesthetics, when used in the formulations for percutaneous administration according to the invention, include lidocaine, benzocaine, lignocaine, methocaine, butylaminobenzoate and procaine or a mixture thereof. A local anaesthetic would mainly be included to suppress the effects of irritation caused at the site of application of a preparation according to the invention. Suitable anti-irritant agents may also be used such as allantoin, corticosteroids, antihistamines and combinations thereof.

Particularly preferred rubifacients, when used in the formulations for percutaneous administration according to the invention, include camphor and menthol or a mixture thereof and other locally acting peripheral vasodilators.

The formulations for percutaneous administration according to the invention are preferably applied to the flexor surface of the forearm, including the wrist, and also the ankle. Such sites of application show the greatest consistency from individual to individual in terms of drug absorption relative to other sites for administration because of the amount of tissue at such sites. Blood vessels are found close to the surface of the skin at such sites, which facilitates the uptake of active agent into the systemic circulation.

On contact of a formulation for percutaneous administration according to the invention with the skin, the active agent starts to migrate rapidly from the formulation to the humid interface at the point of contact and thence through the skin into the bloodstream. The rate and extent of this percutaneous absorption is dependent on several factors including: the amount of active agent in the formulation; and the surface area of the formulation.

As it is the skin itself that forms the rate controlling barrier and not the dosage form comprising the formulation, the effect of active agent loading will only be observed in terms of systemic active agent levels below a threshold loading level. Below this threshold the amount of active agent in the dosage form is the factor which determines the concentration gradient that in turn controls the rate of absorption. Above this threshold increasing drag loading has no effect on absorption as the ability of the skin to absorb the active agent is saturated. However, such drag loading does have the effect of prolonging the time course of drug delivery by providing a larger drug depot. In order to increase the extent of absorption above the threshold it is necessary to increase the area of absorption by increasing the surface area of the dosage form so that a larger area of the skin is in contact with the active agent.

The formulations for percutaneous administration according to the invention can be presented in a number of devices and dosage forms for the percutaneous administration of the active agent. These devices and dosage forms optionally contain an active agent impermeable layer so as to cause undirectional administration of the active agent through the skin from the surface of the formulation in the device or dosage form exposed to the skin. Such devices and dosage forms include, but are not limited to, a device known under the name DERMAFLEX and which is the subject of our EP-B-0 133 562, devices of the type wherein the drug is contained in a drug reservoir which is separated from the skin by a rate-limiting membrane, self adhesive patches, bandages and plasters, creams, gels, jellies, mucilages, ointments and pastes. The term mucilaginous medium as used herein embraces creams, gels, jellies, ointments and pastes.

The formulations for percutaneous administration according to the invention may be adapted for reception in a receptacle of a device which can be held in contact with the skin.

Means for securing transdermal patches to the body include, apart from adhesive means, straps, bracelets and like securing devices.

The present invention is also designed to provide, through percutaneous administration by way of the said devices and dosage forms, a highly cosmetically and aesthetically acceptable method of easily and discretely administering the active agent to a patient.

In certain cases such as: when the patient is applying a formulation for percutaneous administration according to the invention for the first time or when an individual, who has a particularly high requirement for the active agent is

replacing the existing dose, an initial 'burst' or priming dose of active agent may be required to achieve rapid effective plasma levels. The priming dose can be supplied by applying a device or dosage form in which an amount of active agent is included in a layer of adhesive which is used to affix said device or dosage form to the skin. A priming dose of active agent may be included in a layer of adhesive material defining the skin contacting surface of the preparation and which layer is freely permeable to the active agent contained in the solid, semi-solid or mucilaginous agar medium of said preparation. Alternatively, the priming dose of active agent may be included in a peripheral layer of adhesive defining part of the skin-contacting surface of the formulation.

In order to form the formulation for percutaneous administration according to the invention the thickening, hardening, setting, gelling, suspending or solidifying agent or a mixture of such agents is added to the solvent(s) at a concentration that will result in a suitably mucilaginous, semi-solid or solid mass. The mixture is mixed and/or heated, depending on the agent used, so as to produce a uniform medium. The active agent is added in the required amount so as achieve an amount of active agent in the formulation formed which is preferably 10–100 mg, more especially 25–75 mg. Any other inactive ingredients and auxiliary agents as hereinbefore specified are then added and the entire mixture is mixed to uniformity. This mixture is used to form the final dosage form which may be any of the following:

(a) a solid or semi-solid disc or patch formed by moulding, cutting, punching or slicing of the mixture.

(b) a cream.

(c) a mucilage.

(d) a gel.

(e) a paste.

(f) a jelly.

(g) an ointment.

The dosage form may be incorporated into any suitable device for attachment to the skin as indicated above.

When the active agent is a mono-aminopyridine, a particularly preferred mono-aminopyridine is 4-aminopyridine. When the active agent is a di-aminopyridine, a particularly preferred di-aminopyridine is 3,4-DAP.

As stated above, it is believed that 4-AP and 3,4-DAP slow or block the potassium ion flow in nerve impulse transmission. The active agent, therefore, may also be any one of the group of compounds classified as potassium channel blockers, including but not limited to phencyclidine, tetraethylammonium bromide, tetraethylammonium chloride, procaine, quinidine, apamin, amantadine and edrophonium chloride.

The invention also provides a method for the treatment of a neurological disease characterised by a slowing of nerve impulse transmission, which comprises administering to a patient a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit release of said active agent in a manner which achieves therapeutically effective blood levels over a 12–24 hour period when administered on a once- or twice-daily basis.

The mono- or di-aminopyridine active agent is particularly suitable for use in the treatment of a neurological disease which is characterised by demyelination of the central nervous system, more especially multiple sclerosis.

The mono- or di-aminopyridine active agent in accordance with the invention is also suitable for the treatment of Alzheimer's disease.

In one embodiment the medicament is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of said active agent at selected intervals of time until a therapeutic dose is achieved.

In this embodiment of the invention at the commencement of treatment the active agent is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. Suitably when said tolerable state is reached, the dose administered is increased by amounts of at least 5–15 mg/day until said therapeutic dose is reached.

The active agent is preferably 4-aminopyridine or 3,4-diaminopyridine.

The medicament is suitably formulated as a pharmaceutical formulation as hereinbefore specified.

In certain circumstances, the attending physician may consider it appropriate to administer the active agent both orally and percutaneously either simultaneously, separately or sequentially to achieve maximum therapeutic blood levels of said active agent.

The invention will be further illustrated by the following Examples.

EXAMPLES 1

4-AP (8.0 Kg), talc (12.0 Kg) and lactose (36.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. The powder was applied to starch/sugar seeds (0.4–5.0 ram) (12.0 Kg) using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol to form the cores.

A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT S in acetone/ isopropanol 40:60	100 parts by weight
Isopropanol	100 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 68.0 Kg of cores to achieve the dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	0.4
4	34.9
8	68.7
12	85.4
24	99.4

The coated beads were blended with active (rapid release) beads in a ratio of 15:85 of active:coated beads by content of 4-AP to generate the following in vitro dissolution profile:

Time	% Release
1	14.9
4	42.7
8	73.6
12	89.3
24	100.2

EXAMPLE 2

4-AP (4.0 Kg), talc (6.0 Kg) and lactose (18.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. This powder blend was layered into spherical cores using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol.

A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/ isopropanol 40:60	50 parts by weight
12.5% EUDRAGIT S in acetone/ isopropanol 40:60	50 parts by weight
Isopropanol	100 parts by weight

while at the same time but separately dusting on talc (100 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 28.0 Kg of cores to achieve the dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	1.6
4	25.5
8	58.5
12	79.6
24	97.0

On blending with 20% of active beads based on total content of 4AP the following dissolution profile resulted:

Time	% Release
1	19.7
4	40.9
8	64.9
12	81.2
24	96.8

EXAMPLE 3

The procedure used was the same as that outlined in Example 2 with the exception that the active beads were formed in a Glatt fluidised coating apparatus.

The active pellets were coated on the Glatt apparatus with a mixture of polymers comprising EUDRAGIT RS:EUDRAGIT S in the ratio 1:2 to achieve the following release profile:

Time	% Release
1	2.5
4	29.9
8	69.5
12	96.2

These pellets were combined with rapid release pellets in a ratio of 30:70 to generate the following release rates:

Time	% Release
1	30.9
4	49.7
8	77.6
12	97.4

EXAMPLE 4

The active pellets from Example 3 were coated in a Glatt fluidised bed apparatus using a dispersion of EUDRAGIT polymers in water and containing talc and triacetin. The EUDRAGIT polymers consisted of a ratio of 19:1 of EUDRAGIT RS 30D to EUDRAGIT RL D by weight of polymer and the total solid content of the polymer dispersion, including the lubricant (talc) and plasticizer (triacetin) was 23.5%. Following coating and drying, the dissolution rate of the beads according to type II USP apparatus was as follows:

Time	% Release
1	4.6
4	39.5
8	61.2
12	76.6
24	86.2

When blended with active beads in a ratio of 25:75 of active:coated beads by total content of 4-AP the following dissolution profile in the same apparatus was achieved:

Time	% Release
1	28.6
4	54.6
8	70.9
12	82.5
24	91.4

EXAMPLE 5

Active 4-AP beads/pellets were formulated according to the procedure set out in Example 1. These active pellets were coated according to the procedure set out in Example 2, however, the application of coats was such as to provide a form of 4-AP suitable for twice daily administration. The dissolution profile of the coated beads was as follows:

Time	% Release
1	23.6
4	45.2
8	76.4
12	96.2

EXAMPLE 6

Pellets obtained in Example 2 were further coated to the following dissolution rate:

Time	% Release
1	1.9
4	21.3

-continued

Time	% Release
8	53.7
12	83.4

On blending with active 4-AP beads in a ratio of 30:70 of active:coated by content of 4-AP, the following dissolution profile resulted:

Time	% Release
1	31.6
4	44.2
8	66.8
12	89.1

EXAMPLE 7

4-AP (12.0 Kg), talc (8.0 Kg) and lactose (24.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. The powder was applied to starch/sugar seeds (0.5–0.6 mm) (16.0 Kg) using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol to form the cores.

A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/ isopropanol 40:60	100 parts by weight
Isopropanol	50 parts by weight

while at the same time but separately dusting on talc (50 parts by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.41 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 60.0 Kg of cores to achieve the dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	1.6
4	29.8
8	59.4
12	77.7
24	92.8

The coated beads were blended with active (rapid release) beads in a ratio of 20:80 of active:coated beads by content of 4-AP to generate the following in vitro dissolution profile:

Time	% Release
1	21.3
4	43.9
8	66.5
12	82.4
24	93.7

EXAMPLE 8

3,4-DAP (8.0 Kg), talc (12.0 Kg) and lactose (36.0 Kg) were blended and milled through a mill equipped with a 50 mesh screen so as to obtain a homogeneous powder. This powder blend was layered into spherical cores using a Freund CF granulator and a coating solution of 3.5% polyvinylpyrrolidone in isopropanol.

A membrane was then applied to the cores by spraying on a solution consisting of:

12.5% EUDRAGIT RS in acetone/ isopropanol 40:60	50 parts by weight
12.5% EUDRAGIT S in acetone/ isopropanol 40:60	50 parts by weight
Isopropanol	100 parts by weight

while at the same time but separately dusting on talc (100 pans by weight) in conventional manner. The ratio of membrane solution to talc applied was 0.62 g of talc per gram of membrane solution. A sufficient amount of membrane solution and talc was applied to 56.0 Kg of cores to achieve the dissolution profile given below.

The finished pellets were dried to evaporate all solvents prior to performing the dissolution profile.

The dissolution rate of the pellets was tested by method II for the U.S. Pharmacopoeia XXII in water at 50 r.p.m. The dissolution rate was as follows:

Time	% Release
1	3.7
4	29.6
8	51.4
12	72.6
24	98.4

On blending with 25% of active beads based on total content of 3,4-DAP the following dissolution profile resulted:

Time	% Release
1	28.2
4	44.3
8	64.2
12	77.1
24	99.3

EXAMPLE 9

The procedure used was the same as that outlined in Example 2 with the exception that the active beads were formed in a Glatt fluidised coating apparatus.

The active beads were coated on the Glatt apparatus with a mixture of polymers comprising EUDRAGIT RS:EUDRAGIT S in the ratio 1:2 to achieve the following release profile:

Time	% Release
1	3.6
4	28.6
8	60.9
12	88.8

These pellets were combined with rapid release pellets in a ratio of 30:70 to generate the following release rates:

Time	% Release
1	29.7
4	50.1
8	69.3
12	90.4

EXAMPLE 10

The active beads from Example 3 were coated in a Glatt fluidised bed apparatus using a dispersion of EUDRAGIT polymers in water and containing talc and triacetin. The EUDRAGIT polymers consisted of a ratio of 9:1 of EUDRAGIT RS 30D to EUDRAGIT RL 30D by weight of polymer and the total solid content of the polymer dispersion, including the lubricant (talc) and plasticizer (triacetin) was 18.5%.

Following coating and drying, the dissolution rate of the beads according to type II USP apparatus was as follows:

Time	% Release
1	7.6
4	41.4
8	65.2
12	77.4
24	92.6

When blended with active beads in a ratio of 15.8 of active:coated beads by total content of 4-AP the following dissolution profile in the same apparatus was achieved:

Time	% Release
1	22.5
4	50.7
8	72.6
12	79.3
24	93.7

EXAMPLE 11

To 18.3 g of water was added 0.7 g of carrageenan. This mixture was heated to boiling and then allowed to cool gradually. While still in its liquid state 1.0 g of 4-AP was added and the mixture was agitated to ensure uniformity. 1.0 g portions of the gel, equivalent to 50 mg of 4-AP, were weighed into a preformed circular device of internal diameter 3.2 cm giving a surface area of 8 cm^2.

EXAMPLE 12

Patches were prepared as per Example 11 except that 0.5 g of gel was weighed into a preformed circular device of internal diameter 2.3 cm giving a surface area of 4 cm^2.

EXAMPLES 13

Patches were prepared as per Example 11 except that 1.5 g of gel was weighed into a preformed circular device of internal diameter 3.9 cm giving a surface area of 12 cm^2.

EXAMPLE 14

To 100 g of water was added 10 g of powdered gelatin and 10 g of dextrin. The mixture was heated to boiling. While mixing, the following were also added, 0.01 g of benzalkonium chloride, 0.1 g of sodium metabisulphite, 4.8 g of 4-AP. The hot liquid was poured onto preformed circular discs. Each disc weighed 0.65 g with a surface area of 8 cm^2 and each containing 25 mg of 4-AP.

EXAMPLE 15

A product was made as per Example 11 with 0.05 g of methylparaben added to the hot water/carrageenan mixture.

EXAMPLE 16

50 g of stearyl alcohol and 50 g of white petrolatum were melted by heating to 75° C. 0.05 g of methylparaben, 0.3 g of propylparaben, 2 g of sodium lauryl sulphate, 24 g of propylene glycol and 8 g of 4-AP were dissolved in 84 g of water. The aqueous solution was heated to 75° C. and added to the melted stearyl alcohol/petrolatum mixture. The entire mixture was allowed to cool with constant stirring and congealed into a uniform cream. 0.5 g portions of the cream, equivalent to 20 mg of 4-AP, were weighed into circular transdermal delivery devices of internal diameter 2.75 cm giving a surface area of 6 cm^2.

EXAMPLE 17

A product was made as per Example 11 except that 1.4 g of 4-AP was added to the water/carrageenan mixture and the patch was cut into rectangular patches measuring 3x4 cm, each weighing 0.9 g with a surface area of 12 cm^2.

EXAMPLE 18

To 20 g of water was added 0.8 g of agar. This mixture was heated and allowed to cool gradually, while still in its liquid state 1.1 g of 3,4-diaminopyridine was added and the mixture was agitated to ensure uniformity. The liquid mixture was then poured onto several 20 cmx20 cm glass plates equipped with TEFLON (TEFLON is a Trade Mark) dividers approximately 1.31 mm in height. A second similar glass plate was placed over the liquid supported by the TEFLON dividers. The liquid was allowed to cool to room temperature and solidified into a sheet of uniform thickness (approximately 1.31 mm in thickness). The sheet was then cut into discs, each weighing approximately 0.76 g with a surface area of 5.3 cm^2 and each containing 50 mg of 3,4-diaminopyridine. The patches were wrapped in aluminium foil to prevent dehydration.

EXAMPLE 19

To 20 g of water was added 0.8 g of agar. This mixture was heated and allowed to cool gradually, while still in its liquid state 1.11 g of 4-AP was added and the liquid agitated to ensure uniformity. The mixture, while still in the liquid state, was poured into a formed coated aluminium die resulting in a disc of gel of 1.31 mm in thickness and surface area of 5.3 cm^2 following solidification and edged around the circumference by 1 cm of aluminium foil. The disc so prepared was then sealed by a coated foil circular seal edged by 1 cm of adhesive. On removal of the seal the disc selectively adhered to the adhesive side of the device, and the aluminium die in which the disc was formed was

discarded. The device so prepared provides excellent skin contact in use.

EXAMPLE 20

A product was made according to Example 19 except that the 0.8 g of agar was added to a 20 g 15:5 (w/w) mixture of water and glycerol.

EXAMPLE 21

A product was made according to Example 19 except that the 0.8 g of agar was added to a 20 g 90:10 (w/w) water:ethanol mixture.

EXAMPLE 22

A device was prepared as in Example 19 having a 3,4-diaminopyridine concentration of 60 mg/g with a surface area of 7.64 cm^2 and thickness of 1.31 mm.

EXAMPLE 23

A device was prepared as in Example 19 with 0.05 g of methylparaben added to the hot water: agar mixture.

EXAMPLE 24

A device was prepared as in Example 19 with a 15:5 (w/w) mixture of water: PEG (polyethylene glycol) 400 in place of water.

EXAMPLE 25

500 g of water was heated to boiling. 25 g of carrageenan was added and the mixture was boiled for approximately 5–10 minutes. The solution was allowed to cool to between 50 and 60° C. 66 g of 4-AP was added and allowed to dissolve. The solution was diluted to 1,000 g with water. The mixture while still in its liquid state was poured (0.9091 g) into a formed coated aluminium die. The resulting solidified disc had a thickness of 1.30 mm, a surface area of 7.0 cm^2 and contained 60 mg of 4-AP. The formed disc was sealed by a circle of aluminium coated with an impervious membrane and a coat of gelatin. On removal of the seal, the disc selectively adhered to the gelatin side of the aluminium seal. Adhesive tape is used to secure the disc to the skin.

EXAMPLE 26

Patches were prepared as in Example 25 except that 55 g of 4-AP was added yielding finished patches of 50 mg/disc.

EXAMPLE 27

Patches were prepared as in Example 25 except that 12.5 g of agar was added instead of 25 g of carrageenan.

EXAMPLE 28

Patches were prepared as in Example 27 except that water: ethanol, 90: 10, was used in place of water.

IN VITRO STUDY

The rate of transfer of 4-AP across skin from a disc of the type as prepared in Example 11 was determined in a Franz Cell (Franz, T. J., (1975); J. Invest Dermatol. 64,190) using hairless mouse skin at 37° C and a phosphate buffer at pH 7.4. The 4-AP transported through the skin was assayed by HPLC. The results are shown in the accompanying Figure.

We claim:

1. A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12–24 hour period when administered on a once- or twice-daily basis.

2. A method according to claim 1, wherein the neurological disease is characterised by demyelination of the central nervous system.

3. A method according to claim 1 or 2, wherein the neurological disease is multiple sclerosis.

4. A method according to claim 1, wherein the neurological disease is Alzheimer's disease.

5. A method according to claim 1, wherein the medicament is administered to a subject at a dose and for a period sufficient to allow said subject to reach a tolerable state such that said subject is able to tolerate said dose without showing any adverse effects and thereafter increasing the dose of said mono- or di-aminopyridine active agent at selected intervals of time until a therapeutic dose is achieved.

6. A method according to claim 5, wherein at the commencement of treatment the mono- or di-aminopyridine active agent is administered at a dose of less than 15 mg/day until a tolerable state is reached.

7. A method according to claim 5, wherein at the commencement of treatment the mono- or di-aminopyridine active agent is administered at a dose of less than 15 mg/day until a tolerable state is reached and when said tolerable state is reached, the dose administered is increased by amounts of at least 5–15 mg/day until said therapeutic dose is reached.

8. A method according to claim 1, wherein the active agent is 4-aminopyridine.

* * * * *

Patent Assignment Abstract of Title

2

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Application #: 07786400 **Filing Dt:** 11/01/1991 **Patent #:** NONE **Issue Dt:**

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Assignors: MASTERSON, JOSEPH G. **Exec Dt:** 11/05/1991

MYERS, MICHAEL **Exec Dt:** 11/05/1991

Assignee: ELAN CORPORATION, PLC
MONKSLAND INDUSTRIAL ESTATE
ATHLONE, COUNTY WESTMEATH, IRELAND

Correspondent: MARLA J. CHURCH
ELAN PHARMACEUTICAL RESEARCH CORP.
1300 GOULD DR.
GAINESVILLE, GA 30504

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PATENT 91.1806.US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☒ In re application of*: Joseph Gerard Masterson and Michael Myers
Serial No.: 07/ 786,400 Group No.
Filed: November 1, 1991 Examiner:
For*: Formulations and their use in the treatment of neurological diseases
☐ Patent: Issued:

*NOTE: Insert name(s) of inventor(s) and title also for patent. Where recordal is with respect to a maintenance fee payment also insert application serial number and filing date and add Box M. Fee to address.

Commissioner of Patents and Trademarks
Washington, D.C. 20231

RECORDAL OF ASSIGNMENT (37 CFR 1.331)

1. Kindly record the enclosed assignment for the above identified
   - ☒ application
   - ☐ patent
2. When recordal has been effected, please return the original assignment document to the undersigned.
3. Change of patent maintenance fee address

(complete if applicable)

☐ A change of address to which correspondence is to be sent regarding patent maintenance fees for the patent listed above is being sent separately.

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Donna L. Jackson
(Type or print name of person mailing paper)

Date December 12, 1991

Donna L. Jackson
(Signature of person mailing paper)

050 LP 12/27/91 07786400 1 518 8.00 CK

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4. Fee Payment (37 CFR 1.21(h))

☒ Attached is a check in the sum of $8.00.

☐ Charge Account No. _____ the sum of $8.00. A duplicate of this recordal request is attached.

NOTE: 37 CFR 1.21(h). For recording each assignment, agreement or other paper relating to the property in a patent or application, per property, $8.00.

Marla J. Church

SIGNATURE OF ATTORNEY

Marla J. Church

Type or print name of attorney

Elan Pharmaceutical Research Corp.

P.O. Address

1300 Gould Drive, Gainesville, GA 30504

Tel. No. (404) 534-8239

Reg. No. 29,908

REEL: 3960 FRAME: 061

ASSIGNMENT OF APPLICATION FOR PATENT

WHEREAS:

NAME(S) AND ADDRESS(ES) OF INVENTOR(S)

Joseph Gerard Masterson, 33 Rosaville Road, London SW6 7BH, United Kingdom; and Michael Myers, 71, Retreat Park, Athlone, County Westmeath, Ireland

(hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled:

TITLE OF INVENTION

FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

for which application for Letters Patent of the United States has been filed on November 1, 1991

PARTICULARS OF APPLICATION

under Serial No. 07/786,400 , and

WHEREAS:

NAME AND ADDRESS OF ASSIGNEE

Elan Corporation, plc
Monksland Industrial Estate
Athlone, County Westmeath, Ireland

(hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and the United States Letters Patent to be obtained therefor:

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE to ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention and all Letters Patent of the United States to be obtained therefor on said application or

any continuation, division, renewal, substitute or reissue thereof for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain and enforce said application, said invention and said Letters Patent which may be necessary or desirable to carry out the purposes hereof.

IN WITNESS WHEREOF, have hereunto set hand and seal this day of November 5th, 1991

FULL NAME(S) OF INVENTOR(S)

Joseph Gerard Masterson

JOSEPH GERARD MASTERSON

Michael Myers

MICHAEL MYERS

REEL 5960 FRAME 063

Instruction sheet for assignment

All information, names of inventor(s) and assignee, title of invention and particulars of application should be completed.

Signing

No witnessing or legalization is necessary. However, if this assignment is legalized then it will only be prima facie evidence of the execution of the assignment.

Patent Assignment Abstract of Title

3

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 5540938 **Issue Dt:** 07/30/1996 **Application #:** 08328165 **Filing Dt:** 10/24/1994

Inventors: JOSEPH G. MASTERSON, MICHAEL MYERS

Title: FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

Assignment: 1

Reel/Frame: 021266 / 0957 **Recorded:** 07/23/2008 **Pages:** 14

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignor: ELAN CORPORATION, PLC **Exec Dt:** 12/31/2006

Assignee: ELAN PHARMA INTERNATIONAL LIMITED
MONKSLAND
ATHLONE CO.
WESTMEATH, IRELAND

Correspondent: LINDETTE C. THORNTON
2000 MARKET STREET
TENTH FLOOR
PHILADELPHIA, PA 19103

Search Results as of: 02/24/2010 10:01 AM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350.
Web interface last modified: October 18, 2008 v 2.0.1

US005540938A

United States Patent [19]

Masterson et al.

[11] Patent Number: 5,540,938

[45] Date of Patent: Jul. 30, 1996

[54] FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES

[75] Inventors: Joseph G. Masterson, London, United Kingdom; Michael Myers, Athlone, Ireland

[73] Assignee: Elan Corporation, plc, Athlone, Ireland

[21] Appl. No.: 328,165

[22] Filed: Oct. 24, 1994

Related U.S. Application Data

[62] Division of Ser. No. 786,400, Nov. 1, 1991, abandoned, and a division of Ser. No. 73,651, Jun. 7, 1993, Pat. No. 5,370,879.

[51] Int. Cl.[6] A61K 9/16; A61K 9/50; A61K 9/62; A61K 9/70

[52] U.S. Cl. 424/490; 424/445; 424/449; 424/451; 424/452; 424/458; 424/460; 424/461; 424/464; 424/465; 424/474; 424/475; 424/480; 424/484; 424/489; 424/494; 424/495; 424/497; 424/498; 424/499

[58] Field of Search 424/445, 449, 424/451, 452, 458, 460, 461, 464, 465, 474, 475, 480, 484, 489, 494, 495, 497, 498, 499

[56] References Cited

PUBLICATIONS

Davis et al., "D. of the Rush Multiple Sclerosis Center".

Bever et al., Ann. Neurol. 27(4), pp. 421–427 (Apr. 1990).

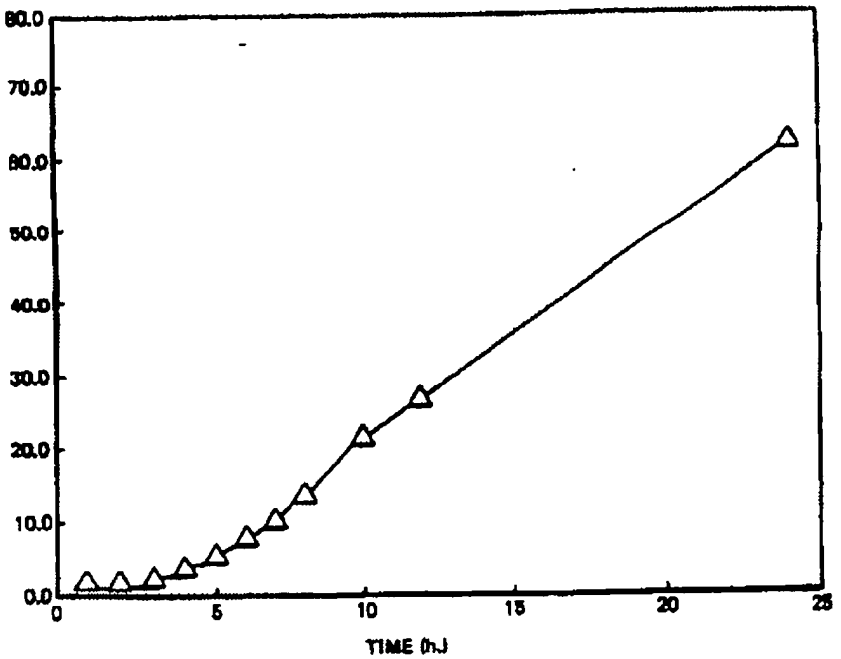
Wesseling et al., N. Eng. J. of Med., 310(15), pp. 988–989 (Apr. 1984).

Primary Examiner—Thurman Page
Assistant Examiner—Carlos Azpuru
Attorney, Agent, or Firm—Marla J. Church

[57] ABSTRACT

Pharmaceutical formulations comprise a mono- or di-aminopyridine active agent for administration on a once- or twice-daily basis for use in the treatment of neurological diseases, in particular multiple sclerosis and Alzheimer's disease. The formulations, which are suitable for oral or percutaneous administration of the active agent, include the active agent in a carrier effective to permit release of the mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12–24 hours following administration.

8 Claims, 1 Drawing Sheet



PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Elan Corporation, PLC	12/31/2006

RECEIVING PARTY DATA

Name:	Elan Pharma International Limited
Street Address:	Monksland
Internal Address:	Athlone Co.
City:	Westmeath
State/Country:	IRELAND

PROPERTY NUMBERS Total: 4

Property Type	Number
Patent Number:	4917899
Patent Number:	5370879
Patent Number:	5540938
Patent Number:	5580580

CH $160.00 4917899

CORRESPONDENCE DATA

Fax Number: (215)299-2150
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 215-299-2186
Email: lthornton@foxrothschild.com
Correspondent Name: Lindette C. Thornton
Address Line 1: 2000 Market Street
Address Line 2: Tenth Floor
Address Line 4: Philadelphia, PENNSYLVANIA 19103

ATTORNEY DOCKET NUMBER:	34074
NAME OF SUBMITTER:	Lindette C. Thornton

Total Attachments: 12
source=Assignment_between__Elan_Corporation__PLC_and_Elan_Pharma_Inter_I_Limited#page1.tif
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THIS DEED OF ASSIGNMENT, dated 31 December, 2006 is made

BETWEEN:

(1) ELAN CORPORATION, PLC, a public limited company incorporated under the laws of Ireland, and having its registered office at Treasury Building, Lower Grand Canal Street, Dublin 2, Ireland (the "Assignor"); and

(2) ELAN PHARMA INTERNATIONAL LIMITED, a private limited company incorporated under the laws of Ireland, and having its registered office at Monksland, Athlone Co. Westmeath, Ireland (the "Assignee").

BACKGROUND:

(A) The Assignor is the legal and beneficial owner of certain drug delivery technologies (the "Technologies") used or useful in the development, manufacture and administration of pharmaceutical products displaying certain delivery or release characteristics. Various aspects of the Technologies are protected by patents and / or are the subject of currently pending patent applications, hereinafter "the Patents" (including without limitation those set out in Schedule 1 hereto). The Assignor also owns certain know-how ("the Know-How") relating to the Technologies. The Assignor also owns various trade marks relating to or used in connection with the Technologies, together with the associated goodwill hereinafter "the Trade Marks" (as set out in Schedule 2 hereto, together with any other registrations and applications for registration in any country of the world of any of the trade marks listed in Schedule 2). The Patents, the Know-How and the Trade Marks collectively are hereinafter referred to as the "Intellectual Property Rights".

(B) The Assignor has actively engaged in out licensing the Technologies and related Intellectual Property Rights to third parties, in return for which the Assignor receives certain ongoing royalties and other payments. In particular the Assignor has entered into various licences with third parties [redacted] to operate under or use some or all of the Intellectual Property Rights.

(C) The Assignor now wishes to transfer the Intellectual Property Rights and (to the extent Assignor is permitted to do so under the terms of the relevant agreements) its rights, duties, obligations and liabilities arising under or related to the Existing Licences to the Assignee on the terms set out below.

THE PARTIES AGREE as follows:

1. ASSIGNMENT:

In consideration of the payment of an amount equal to the book value of the Intellectual Property rights and associated assets and liabilities as at the effective date

(receipt of which is hereby acknowledged), the Assignor assigns and transfers (to the extent Assignor is permitted to do so) to the Assignee, and the Assignee accepts such assignment and transfer, all right, title and interest in the Intellectual Property Rights and all the Assignor's rights, duties, obligations and liabilities arising under or related to the Existing Licences (whether accrued and / or present or future and / or actual or contingent).

2. UNDERTAKING:

2.1. To the extent that the Assignor cannot assign any Intellectual Property Rights to the Assignee, it is agreed that any such right (including, where applicable, any moral right, such as a right of paternity or integrity) shall be irrevocably and unconditionally waived by the Assignor, and shall not be exercised against the Assignee, or any person deriving an interest therein through the Assignee including its assignees and licensees.

2.2. The Assignor hereby agrees not to communicate or otherwise make available the Know-How to any third party without the prior written consent of the Assignee, nor use the Know-How for any purpose.

2.3. The Assignor warrants that, except for the Assignee, certain third parties and certain employees of the Assignor (all of whom are subject to an enforceable obligation of confidentiality), the Know-How has not been disclosed to any person, firm or company.

2.4. The Assignor shall provide the Assignee with such explanations concerning the Know-How as the Assignee reasonably requires.

3. GOVERNING LAW AND JURISDICTION:

3.1 This Deed of Assignment and all matters arising out of or in connection with it are governed by Irish law.

3.2 The courts of Ireland have exclusive jurisdiction to settle any dispute arising out of or in connection with this Deed of Assignment.

EXECUTED by the parties as a deed and delivered on the date written at the start of this Deed of Assignment

Executed as a Deed by:

ELAN CORPORATION, PLC

By: .....

Name: Liam Daniel.....

Title: EVP & Company Secretary

Witnessed by: Noel Kehoe

Name: NOEL KEHOE.....

Title: .....

ELAN PHARMA INTERNATIONAL LIMITED

By: .....

Name: Liam Daniel.....

Title: EVP & Company Secretary

Witnessed by: Noel Kehoe

Name: .....

Title: .....

SCHEDULE 1. Patents.

Title / Elan Family	Territory	Number
SCREENING METHOD AND APPLICATION THEREOF – DETECTION OF DHEA IN HIV INFECTION Elan 0700	France United Kingdom Italy	9,111,118 2,249,833 1,255,009
TAMER RESISTANT MATRIX OPIATE COMPOSITION – ABUSE RESISTANT PHARMACEUTICAL COMPOSITIONS (jointly owned with Verion, Inc) Elan 1005	Pending Canada EP Application* Japan United States Published WIPO	 2,499,994 1551402 20040538423 10/528,727 PCT/US03/029890
TOPIRAMATE PHARMACEUTICAL COMPSITION Elan 1010	Pending United States PCT	 11/297,737 PCT/US05/44315
TABLET FORMULATION Elan 1808	Pending Japan	 20050225315
DRUG DELIVERY SYSTEM Elan 1100	Australia Belgium Canada Denmark [illegible] Germany Ireland Italy Japan Netherlands New Zealand Philippines Philippines South Africa Spain Sweden Switzerland United Kingdom United States United States	598514 0232155 1,288,344 PR173082 [illegible] 0232155 63321 0232155 2527432 0232155 219139 24331 27654 87/0737 0232155 0232155 0232155 0232155 5,128,142 4,973,469

SUSTAINED RELEASE CAPSULE OR TABLET FORMULATION (NIFEDIPINE) Elan 1150	Australia Belgium Canada Denmark European Patent France Germany Ireland Italy Japan Netherlands New Zealand Philippines South Africa Spain Sweden Switzerland United Kingdom United States	592618 0274176 1,288,049 PR172893 0274176 0274176 0274176 59540 0274176 2763879 0274176 219140 23528 87/0738 0274176 0274176 0274176 0274176 5,015,479
CONTROLLED RELEASE POWDER AND PROCESS FOR ITS PREPARATION Elan 1250	United States United States United States	4,940,588 4,952,402 5,354,556
LIQUID SUSPENSION FOR ORAL ADMINISTRATION Elan 1251	Belgium Canada Denmark European Patent France Germany Ireland Italy Luxembourg Netherlands Philippines Spain Sweden United Kingdom	0295941 1,314,215 175812 0295941 0295941 0295941 59934 0295941 0295941 0295941 24979 0295941 0295941 0295941
TASTE-MASKED FORMULATIONS Elan 1254	Canada Japan South Africa United States	2,304,630 2000-514619 98/9013 6,153,220
"CONTROLLED RELEASE BIODEGRADABLE MICRO- AND NANOSPHERES CONTAINING CYCLOSPORIN" Elan 1255	Austria Australia Belgium Denmark European Patent Finland France Germany Greece Ireland	0818996 700612 0818996 0818996 0818996 0818996 0818996 0818996 0818996 75744

	Italy	0818996
	Luxembourg	0818996
	Monaco	0818996
	Netherlands	0818996
	New Zealand	304975
	Portugal	0818996
	South Africa	96/2670
	Spain	0818996
	Sweden	0818996
	Switzerland	0818996
	United Kingdom	0818996
	United States	5,641,745
	Pending	
	Canada	2,217,462
	Japan	530156/96
	Published	
	WIPO	PCT/IE96/00017
"CONTROLLED RELEASE BIODEGRADABLE NANOPARTICLES CONTAINING INSULIN" Elan 1256	Austria	E261311
	Australia	704875
	Belgium	820300
	Denmark	820300
	European Patent	820300
	Finland	820300
	France	820300
	Germany	6982283.5
	Greece	3049047
	Ireland	80468
	Italy	820300
	Luxembourg	820300
	Monaco	820300
	Netherlands	820300
	New Zealand	304976
	Portugal	820300
	South Africa	96/2671
	Spain	820300
	Switzerland	820300
	United Kingdom	820300
	United States	5,641,515
	Pending	
	Canada	2,217,485
	Japan	530157/96
	Published	
	WIPO	PCT/IE96/00018
PHARMACEUTICAL FORMULATION AND METHOD FOR THE CONTROL OF HYPERTENSION AND THE SYMPTOMS OF ANGINA OVER A TWENTY-FOUR HOUR PERIOD Elan 1300	Austria	320097
	Australia	615221
	Australia	634660
	Belgium	320097
	Denmark	175591

	European Patent	320097
	France	320097
	Germany	320097
	Greece	320097
	Italy	320097
	Japan	2091545
	Luxembourg	320097
	Netherlands	320097
	New Zealand	226575
	Philippines	27915
	Portugal	88776
	South Africa	88/7681
	South Korea	118033
	Spain	219483213
	Sweden	320097
	Switzerland	320097
	United Kingdom	320097
	United States	5,002,776
CONTROLLED ABSORPTION DILTIAZEM FORMULATION FOR ONCE-DAILY ADMINISTRATION Elan 1301	United States	4,894,240
	United States	5,364,620
	United States	5,616,345
CONTROLLED ABSORPTION DILTIAZEM FORMULATIONS Elan 1303	Ireland	84002
	United States	4,891,230
	United States	5,219,621
	United States	5,336,504
CONTROLLED ABSORPTION DILTIAZEM FORMULATION Elan 1304	Ireland	60929
	United States	4,917,899
IMPROVEMENTS IN OR TO PROCESSES FOR THE PREPARATION OF DELAYED ACTION PROGRAMMED RELEASE GALENIC FORMS AND GALENIC FORMS OF MEDICAMENTS OBTAINED	United States	5,051,262
CONTROLLED ABSORPTION PHARMACEUTICAL COMPOSITION Elan 1750	Austria	0250267
	Australia	599385
	Belgium	0250267
	European Patent	0250267
	France	0250267
	Germany	0250267
	Greece	0250267
	Ireland	58401
	Italy	0250267
	Japan	2637981
	Luxembourg	0250267
	Netherlands	0250267
	Philippines	23993
	Spain	0250267
	Sweden	0250267
	Switzerland	0250267

	United Kingdom United States	0250267 4,863,742
PREPARATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES Elan 1806	Austria Australia Belgium Canada Denmark European Patent France Germany Greece Ireland Italy Luxembourg Netherlands New Zealand South Africa Spain Sweden Switzerland United Kingdom United States United States United States	0484186 657706 0484186 2,054,822 0484186 0484186 0484186 0484186 20000400471 82916 0484186 0484186 0484186 240439 91/8711 0484186 0484186 0484186 0484186 5,370,879 5,540,938 5,580,580
TABLET FORMULATION Elan 1808	Japan	225315/2005
ORAL MORPHINE MULTI PARTICULATE FORMULATION Elan 1809	Austria Belgium Canada Denmark European Patent Finland France Germany Hong Kong Italy Monaco Netherlands Portugal South Africa Spain Sweden Switzerland Taiwan United Kingdom United States Pending Japan Published	1023051 1023051 2,306,333 1023051 1023051 1023051 1023051 1023051 1023051 1023051 1023051 1023051 98/9463 1023051 1023051 1023051 172439 1023051 6,066,339 2000-516654

	WIPO	PCT/IE97/00082
MULTIPARTICULATE MODIFIED RELEASE COMPOSITION (METHYLPHENIDATE) Elan 1816	Australia Australia Malaysia New Zealand Pakistan Philippines Russia Turkey United States United States United States United States	770645 0202078/04 122159A 511442 137141 99/2721 2236847 2001/01216 6,228,398 6,730,325 6,902,742 6,793,936
	Pending	
	Brazil China Ecuador EP Application* Hungary Vietnam Argentina Australia Canada Chile China Colombia Czech Republic Hong Kong Indonesia Israel Japan Mexico Norway Peru Poland Singapore [illegible] South Korea Taiwan Taiwan Thailand United States United States United States Venezuela	PI9914977-0 99814002.3 SP-99-3198 99956822.3 P014039 1-2001-00390 P990105538 0247019/05 2,348,871 2491-99 02132215.5 99069009 PV2001-1539 30102681.7 W-00200101174 142896 2000-579194 01/004381 2001-2139 001106.99 P348633 200102450-4 [illegible] [illegible] 88119049 95111114 053705 09/432,947 10/827,689 11/372,857 1999-002232
	Published	
	WIPO	PCT/US99/25632
MULTIPARTICULATE CONTROLLED RELEASE SELECTIVE SEROTONIN REUPTAKE INHIBITOR (FLUVOXAMINE) Elan 1819	Australia Ireland Russia South Africa	782059 83094 2275191 2001/10401

	Pending	
	EP Application*	00925548.0
	Hungary	P0201884
	Slovak Republic	PV1896-2001
	Canada	2,374,039
	Czech Republic	PV2001-4618
	Algeria	044/01
	Japan	2000-619406
	Ukraine	2001128821M
	United States	09/744,169
	Published	
	WIPO	PCT/IB00/00060

[* "EP Application" indicates application before the European Patent Office.]

SCHEDULE 2. Trade Marks

Trade Mark	Registration / Application No.
BEODAS	IE 157546
DERMAFLEX	IE 124740 US 1551790
DRUG DELIVERY TREE	CTM 001982115 JP 4589930
DRYDOS	IE 210185 US 2613626
DUREDAS	IE 205247 US 2557523
EFVDAS	CH 405.409 IE 150893
EMDAS	
ERYZOME	IE 130913
ETDAS	IE 140889
EXODUS	AU 562768 AU 562769 CH 393.656 DK 07.220 1993 GB 1480911 IE 146549 IT 610729 NZ 212574 NZ 212629 SG T95/01196D SE 243986
INDAS	IE 127074
IPDAS	IE 148992 US 2110477
LOCDAS	IE 214689
MEDIPAD	GB 2003655 IE 163886 JP 4718655 US 2183377
MICROFUSOR	US 2172083

MIDAS	IE 155604
MINIFUSOR	US 2190161
MODAS	CA A543197 IE 125031
MXDAS	
NANOZOME	IE 133476
PANODERM	IE 124739 US 2148886
PANOJECT	CA 0714839 BS 1758449 IE 142494 IE 142495 IT 664427 JP 4112535
PARELAN	IE 122125
PHARMAZOME	AT 113853 BX 404625 CH 349.080 DE 1111894 DK 1650-1987 ES 1543555M5 FR 1288404 GB 1229083 GR 78576 IE 112820 IT 461403 PT 234575 US 1441001
PRODAS	CA A531459 IE 206703 US 2361023
SODAS	AR 1.724.388 CA A531496 CTM 002012953 IE 125699 JP 3214211 US 2794607
SOLIDOSE	US 2560763
ZOME	IE 137282

(4)

Jane Wasman,
Executive Vice President,
General Counsel & Corporate Secretary
Acorda Therapeutics, Inc.
15 Skyline Drive
Hawthorne, NY 10532

March 15, 2010

VIA HAND DELIVERY

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

Re: Patent Term Extension Applications for United States Patent Nos. 5,540,938 ("the '938 patent") and 5,370,879 ("the '879 patent")

Dear Ms. Till:

On behalf of Acorda Therapeutics, Inc., Marketing Applicant for New Drug Application No. 22-250 for AMPYRA® (dalfampridine), its predecessors, and affiliates, I hereby authorize the patent owner of record, Elan Pharma International Ltd., in connection with its application for extension of U.S. Patent No. 5,540,938, and of U.S. Patent 5,370,879, to rely upon the activities of Acorda Therapeutics, Inc., its predecessors, and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 22-250. Acorda Therapeutics, Inc. is a licensee of the Elan Pharma International Ltd. under the patents.

Respectfully submitted,

Jane Wasman,
Executive Vice President,
General Counsel &
Corporate Secretary
Acorda Therapeutics, Inc.

(5)

élan

Monksland, Athlone,
Co. Westmeath, Ireland.

T (+353 90) 649 5000
F (+353 90) 649 5402

March 16, 2010

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450, Alexandria,
VA 22313-1450

Re: Patent Term Extension Applications for United States Patent Nos. 5,540,938 ("the '938 patent") and 5,370,879 ("the '879 patent")

Dear Ms. Till:

This is to advise you that, as an authorized representative of Elan Pharma International Limited ("**Elan**"), owner of United States Patent Nos. 5,540,938 ("**the '938 patent**") and 5,370,879 ("**the '879 patent**"), I hereby authorize Acorda Therapeutics, Inc. of 15 Skyline Drive, Hawthorne, New York, ("**Acorda**") to file and prosecute patent term extension applications pursuant to 35 U.S.C. § 156 for the '938 and '879 patents ("**the Applications**") on behalf of Elan, pursuant to 37 CFR § 1.730(c).

I understand that counsel for Acorda, Covington & Burling LLP, 1201 Pennsylvania Ave. N.W., Washington, D.C., 20004-2401 (C&B), will file and prosecute the Applications as Acorda's representative, pursuant to 37 C.F.R. § 1.730(c), and hereby grant C&B any authorizations from Elan necessary for C&B to act in this capacity.

Sincerely,

Shane Cooke
Director and Authorised Signatory

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMPYRA safely and effectively. See full prescribing information for AMPYRA.

AMPYRA™ (dalfampridine) Extended Release Tablets, for oral use
Initial U.S. Approval: 2010

INDICATIONS AND USAGE

AMPYRA™ (dalfampridine) is a potassium channel blocker indicated to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed (1, 14).

DOSAGE AND ADMINISTRATION

- Maximum recommended dose: 10 mg twice daily (approximately 12 hours apart) with or without food (2)
- Patients should not take double or extra doses if a dose is missed. No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse events, including seizures, were more frequent at higher doses (2)
- Tablets should only be taken whole; do not divide, crush, chew, or dissolve (2)
- Renal impairment: AMPYRA is contraindicated in patients with moderate or severe renal impairment; the risk of seizures in patients with mild renal impairment is unknown, but AMPYRA plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures (4, 5.1, 5.2)

DOSAGE FORMS AND STRENGTHS

10 mg tablets (3)

CONTRAINDICATIONS

- History of seizure (4)
- Moderate or severe renal impairment (4)

WARNINGS AND PRECAUTIONS

- Seizures: AMPYRA can cause seizures; the risk of seizures increases with increasing AMPYRA doses; AMPYRA is contraindicated in patients with a prior history of seizure; discontinue AMPYRA use if seizure occurs (5.1)
- Renally impaired patients: AMPYRA is contraindicated in patients with moderate to severe renal impairment (CrCl≤50 mL/min); the risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures (4, 5.1, 5.2); estimated CrCl should be known before initiating treatment with AMPYRA (4, 5.2, 8.6)
- AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine), since the active ingredient is the same (5.3)
- Urinary tract infections were reported more frequently as adverse reactions in patients receiving AMPYRA 10 mg twice daily compared to placebo (5.4)

ADVERSE REACTIONS

The most common adverse events (incidence ≥2% and at a rate greater than the placebo rate) for AMPYRA in MS patients were urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Acorda Therapeutics at 1-800-367-5109 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

None identified.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric use: Safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established
- Renal Impairment: Clearance of dalfampridine is decreased in patients with renal impairment; AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl≤50 mL/min); AMPYRA plasma levels in patients with mild renal impairment (CrCl 51–80 mL/min) may approach those seen at a dose of 15 mg twice daily, a dose which may be associated with an increased risk of seizures (4, 5.2, 8.6)
- Geriatric use: Because elderly patients are more likely to have decreased renal function, it is particularly important to know the estimated CrCl in these patients before initiating AMPYRA treatment (4, 5.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMPYRA (dalfampridine) is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The maximum recommended dose of AMPYRA is one 10 mg tablet twice daily, taken with or without food, and should not be exceeded. Doses should be taken approximately 12 hours apart. Patients should not take double or extra doses if a dose is missed.

No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse reactions and discontinuations because of adverse reactions were more frequent at higher doses. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.

AMPYRA is contraindicated in patients with moderate or severe renal impairment *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but AMPYRA plasma exposure in these patients may approach that seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures; estimated CrCl should be known before initiating treatment with AMPYRA *[see Warnings and Precautions, Renal Impairment (5.2) and Clinical Pharmacology, Special Populations (12.4)]*.

[See FDA-Approved Patient Information for complete "Instructions for Use"]

3 DOSAGE FORMS AND STRENGTHS

AMPYRA is available in a 10 mg strength and is a film-coated, white to off-white, biconvex, oval shaped, non-scored tablet with flat edge, debossed with "A10" on one side.

4 CONTRAINDICATIONS

The use of AMPYRA is contraindicated in the following conditions:

- History of seizure
- Moderate or severe renal impairment

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

AMPYRA is contraindicated in patients with a history of seizures *[see Contraindications (4)]*. Increased incidence of seizures has been observed at 20 mg twice daily in controlled clinical studies of 9–14 weeks duration with dalfampridine in patients with MS. There was one seizure seen in the placebo group (0.4%) and at a dose of 10 mg twice daily (0.25%), no seizure seen at 15 mg twice daily and 2 seizures (3.5%) seen at 20 mg twice daily. In open label extension trials in MS patients, the incidence of seizures during treatment with dalfampridine 15 mg twice daily (1.7/100PY) was over 4 times higher than the incidence during treatment with 10 mg twice daily (0.4/100PY).

AMPYRA has not been evaluated in patients with a history of seizures or with evidence of epileptiform activity on an EEG, as these patients were excluded from clinical trials. The risk of seizures in patients with epileptiform activity on EEG is unknown, and could be substantially higher than that observed in AMPYRA clinical studies. AMPYRA should be discontinued and not restarted in patients who experience a seizure while on treatment.

5.2 Renal Impairment

AMPYRA is eliminated through the kidneys primarily as unchanged drug *[see Clinical Pharmacology, Special Populations (12.4)]*.

Because patients with renal impairment would require a dose lower than 10 mg twice daily and no strength smaller than 10 mg is available, AMPYRA is contraindicated in patients with moderate to severe renal impairment [Creatinine Clearance (CrCl) ≤50mL/min] *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but dalfampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures *[see Warnings and Precautions, Seizures (5.1)]*. If unknown, CrCl should be estimated prior to initiating treatment with AMPYRA. CrCl can be estimated using the following equation (multiply by 0.85 for women):

$$CrCl = \frac{(140 - age) \times weight(kg)}{SerumCr(mg/dl) \times 72}$$

5.3 Concurrent Treatment with Other Forms of 4-Aminopyridine

AMPYRA should not be taken with other forms of 4-aminopyridine (4-AP, fampridine) since the active ingredient is the same. Patients should discontinue use of any product containing 4-aminopyridine prior to initiating treatment with AMPYRA in order to reduce the potential for dose-related adverse reactions.

5.4 Urinary Tract Infections

Urinary tract infections were reported more frequently as adverse reactions in controlled studies in patients receiving AMPYRA 10 mg twice daily (12%) as compared to placebo (8%).

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The following adverse reaction is described in more detail in the Warnings and Precautions section of the label: Seizures and Urinary Tract Infections.

6.1 Controlled Clinical Trials Experience

In three placebo-controlled clinical trials of up to 14 weeks duration, 4% (15/400) of patients treated with AMPYRA 10 mg twice daily experienced one or more treatment emergent adverse events leading to discontinuation, compared to 2% (5/238) of placebo-treated patients. The treatment emergent adverse events leading to discontinuation of at least 2 patients treated with AMPYRA and that led to discontinuation more frequently compared to placebo were headache (AMPYRA 0.5%, placebo 0%), balance disorder (AMPYRA 0.5%; placebo 0%), dizziness (AMPYRA 0.5%, placebo 0%), and confusional state (AMPYRA 0.3%, placebo 0%).

Table 1 lists adverse reactions that occurred in ≥2% of patients treated with AMPYRA 10 mg twice daily, and more frequently than in placebo-treated patients, in controlled clinical trials.

Table 1: Adverse reactions with an incidence ≥2% of AMPYRA treated MS patients, and more frequent with AMPYRA compared to placebo in controlled clinical trials

Adverse Reaction	Placebo (N=238)	AMPYRA 10 mg twice daily (N=400)
Urinary tract infection	8%	12%
Insomnia	4%	9%
Dizziness	4%	7%
Headache	4%	7%
Nausea	3%	7%
Asthenia	4%	7%
Back pain	2%	5%
Balance disorder	1%	5%
Multiple sclerosis relapse	3%	4%
Paresthesia	3%	4%
Nasopharyngitis	2%	4%
Constipation	2%	3%
Dyspepsia	1%	2%
Pharyngolaryngeal pain	1%	2%

6.2 Other Adverse Reactions

AMPYRA has been evaluated in a total of 1,952 subjects, including 917 MS patients. A total of 741 patients have been treated with AMPYRA for over six months, 501 for over one year and 352 for over two years. The experience in open-label clinical trials is consistent with the safety profile observed in the placebo-controlled clinical trials. As in controlled clinical trials, a dose-dependent increase in the incidence of seizures has been observed in open-label clinical trials with AMPYRA in patients with MS as follows: AMPYRA 10 mg twice daily 0.41 per 100 person-years (95% confidence interval 0.13–0.96); dalfampridine 15 mg twice daily 1.7 per 100 person-years (95% confidence interval 0.21–6.28).

7 DRUG INTERACTIONS

In humans, dalfampridine is eliminated predominately unchanged by the kidneys. No clinically significant drug interaction was identified *[see Clinical Pharmacology, Pharmacokinetics (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of AMPYRA in pregnant women. Administration of dalfampridine to animals during pregnancy and lactation resulted in decreased offspring viability and growth at doses similar to the maximum recommended human dose (MRHD) of 20 mg/day. AMPYRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In developmental toxicity studies in rats and rabbits, dalfampridine was administered orally at doses up to 10 and 5 mg/kg/day, respectively, during the period of organogenesis. These doses are approximately 5 times the MRHD on a body surface area (mg/m^2) basis. No evidence of developmental toxicity was found in either species at the highest doses tested, which were maternally toxic. Oral administration of dalfampridine (at doses of 1, 3, and 9/6 mg/kg/day; high dose reduced during the second week of dosing) to rats throughout the pregnancy and lactation periods resulted in decreased offspring survival and growth. The no-effect dose for pre- and postnatal developmental toxicity in rats (1 mg/kg) is approximately 0.5 times the MRHD on a mg/m^2 basis.

8.2 Labor and delivery
The effect of AMPYRA on labor and delivery in humans is unknown.

8.3 Nursing mothers
It is not known whether dalfampridine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from dalfampridine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric use
Safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established.

8.5 Geriatric use
Clinical studies of AMPYRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. A population PK analysis showed that dalfampridine clearance modestly decreased with increasing age, but not sufficiently to necessitate a modification of dose with age. Other reported clinical experience has identified no differences in responses between the elderly and younger patients.

AMPYRA is known to be substantially excreted by the kidney and the risk of adverse reactions, including seizures, is greater with increasing exposure of dalfampridine. Because elderly patients are more likely to have decreased renal function, it is particularly important to know the estimated creatinine clearance (CrCl) in these patients *[see Warnings and Precautions, Renal Impairment (5.2)]*.

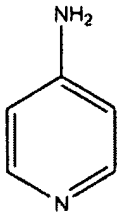
8.6 Impaired Renal Function
Clearance of dalfampridine is decreased in patients with renal impairment and is significantly correlated with creatinine clearance *[see Clinical Pharmacology, Special Populations (12.4)]*. AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl ≤50 mL/min) *[see Contraindications (4)]*. The risk of seizures in patients with mild renal impairment (CrCl 51–80 mL/min) is unknown, but dalfampridine plasma levels in these patients may approach those seen at a dose of 15 mg twice daily, a dose that may be associated with an increased risk of seizures. Creatinine clearance (CrCl) should be calculated prior to initiating treatment with AMPYRA *[see Warnings and Precautions, Renal Impairment (5.2)]*.

9 DRUG ABUSE AND DEPENDENCE
No studies on the abuse or dependence potential of AMPYRA have been performed.

10 OVERDOSAGE
Three cases of overdose were reported in controlled clinical trials with AMPYRA, involving two MS patients. The first patient took six times the currently recommended dose (60 mg) and was taken to the emergency room with altered mental state. The second patient took 40 mg doses on two separate occasions. In the first instance, she experienced a complex partial seizure and, in the second instance, a period of confusion. Both patients recovered by the following day without sequelae.

Several cases of overdose are found in the scientific literature in which various formulations of dalfampridine were used, resulting in numerous adverse events including seizure, confusion, tremulousness, diaphoresis and amnesia. In some instances, patients developed status epilepticus, requiring intensive supportive care and were responsive to standard therapy for seizures. In one published case report, an MS patient who ingested 300 mg of 4-aminopyridine (dalfampridine) developed a condition that resembled limbic encephalitis. This patient developed weakness, reduced awareness, memory loss, hypophonic speech, and temporal lobe hyperintensities on MRI. The patient's speech and language and ambulation improved over time, and an MRI at 4 months after the overdose no longer showed signal abnormalities. At one year, the patient continued to have difficulty with short term memory and learning new tasks.

11 DESCRIPTION
AMPYRA (dalfampridine) is a potassium channel blocker, available in a 10 mg tablet strength. Each tablet contains 10 mg dalfampridine, formulated as an extended release tablet for twice-daily oral administration. Dalfampridine is also known by its chemical name, 4-aminopyridine, with the following structure:



AMPYRA (dalfampridine) Extended Release tablets are available in a 10 mg strength and are a white to off-white, biconvex, oval shaped, film-coated, non-scored tablet with flat edge, debossed with "A10" on one side, containing 10 mg of dalfampridine. Inactive ingredients consist of colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Dalfampridine is a fine white powder with a molecular weight of 94.1, CAS 504-24-5 and a molecular formula of $C_5H_6N_2$. At ambient conditions, dalfampridine is soluble in water, methanol, acetone, tetrahydrofuran, isopropanol, acetonitrile, N,N-dimethylformamide, dimethylsulfoxide, and ethanol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
The mechanism by which dalfampridine exerts its therapeutic effect has not been fully elucidated. Dalfampridine is a broad spectrum potassium channel blocker. In animal studies, dalfampridine has been shown to increase conduction of action potentials in demyelinated axons through inhibition of potassium channels.

12.2 Pharmacodynamics
AMPYRA does not prolong the QTc interval and does not have a clinically important effect on QRS duration.

12.3 Pharmacokinetics
Absorption and Distribution:
Orally administered dalfampridine is rapidly and completely absorbed from the gastrointestinal tract. Absolute bioavailability of extended release AMPYRA tablets has not been assessed, but relative bioavailability is 96% when compared to an aqueous oral solution. The extended release tablet delays absorption of dalfampridine relative to the solution formulation, giving a slower rise to a lower peak concentration (Cmax), with no effect on the extent of absorption (AUC). Single AMPYRA tablet 10 mg doses administered to healthy volunteers in a fasted state gave peak concentrations ranging from 17.3 ng/mL to 21.6 ng/mL occurring 3 to 4 hours post-administration (Tmax). In comparison, Cmax with the same 10 mg dose of dalfampridine in an oral solution was 42.7 ng/mL and occurred approximately 1.3 hours after dosing. Exposure increased proportionally with dose.

Dalfampridine is largely unbound to plasma proteins (97–99%). The apparent volume of distribution is 2.6 L/kg.

There is no apparent difference in pharmacokinetic parameter values following administration of AMPYRA tablets to either healthy volunteers or patients with MS.

When dalfampridine is taken with food, there is a slight increase in Cmax (12–17%) and a slight decrease in AUC (4–7%). These changes in exposure are not clinically significant, and therefore the drug may be taken with or without food *[see Dosage and Administration (2)]*.

Metabolism and Elimination:
Dalfampridine and metabolites elimination is nearly complete after 24 hours, with 95.9% of the dose recovered in urine and 0.5% recovered in feces. Most of the excreted radioactivity in urine was parent drug (90.3%). Two metabolites were identified: 3-hydroxy-4-aminopyridine (4.3%) and 3-hydroxy-4-aminopyridine sulfate (2.6%). These metabolites have been shown to have no pharmacologic activity on potassium channels.

The elimination half-life of dalfampridine following administration of the extended release tablet formulation of AMPYRA is 5.2 to 6.5 hours. The plasma half-life of the sulfate conjugate is approximately 7.6 hours and the half-life of 3-hydroxy-4-aminopyridine could not be calculated because concentrations for most subjects were close to or below the limit of quantitation.

In vitro studies with human liver microsomes indicate that CYP2E1 was the major enzyme responsible for the 3-hydroxylation of dalfampridine. The identity of the CYP enzymes suspected of playing a minor role in the 3-hydroxylation of dalfampridine could not be established unequivocally.

12.4 Special Populations

Pediatric
The safety and effectiveness of AMPYRA in patients younger than 18 years of age have not been established.

Geriatric
A population pharmacokinetic analysis showed that dalfampridine clearance modestly decreased with increasing age, but not sufficiently to necessitate a modification of dose.

Gender
A population pharmacokinetic analysis suggested that female patients would be expected to have higher maximum dalfampridine plasma concentration than male patients. The magnitude of these differences is small and does not necessitate any dose modification.

Renal Impairment *[see Contraindications (4) and Warnings and Precautions, Renal Impairment (5.2)]*.
The pharmacokinetics of dalfampridine was studied in 9 male and 11 female subjects with varying degrees of renal function. Elimination of the drug is significantly correlated with the creatinine clearance. Total body clearance of dalfampridine was reduced by about 45 % in patients with mild renal impairment (CrCl 51–80 mL/min), by about 50% in patients with moderate renal impairment (CrCl = 30–50 mL/min), and by about 75% in patients with severe renal impairment (CrCl <30 mL/min). The terminal half-life of dalfampridine is about 3.3 times longer in patients with severe renal impairment but is not prolonged in patients with mild or moderate renal impairment.

Hepatic Impairment
The pharmacokinetics of dalfampridine in hepatically impaired subjects has not been studied. Since dalfampridine is primarily excreted unchanged in the urine, hepatic impairment is not expected to significantly affect dalfampridine pharmacokinetics or recommended dosing.

Race
There were too few non-Caucasians in the patient population to evaluate the effect of race.

Drug Interactions
Effects of Coadministered Drugs on Dalfampridine
Interferon
Dalfampridine kinetics were not affected by co-administration of subcutaneous injections of 8 million units interferon beta-1b.

Baclofen
No pharmacokinetic drug-drug interaction was observed with co-administration of dalfampridine 15 mg and baclofen 10 mg.

Effects of Dalfampridine on Coadministered Drugs
In vitro data with human liver microsomes showed that dalfampridine was not a direct or time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of these enzymes.

Other *in vitro* studies with cultured human hepatocytes with 0.025 µM, 0.25 µM, 2.5 µM and 25 µM dalfampridine had little or no effect on CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2E1 or CYP3A4/5 enzyme activities. Consequently, the potential for dalfampridine to induce human hepatocytes at therapeutic concentrations is remote.

In vitro, dalfampridine is not a substrate or an inhibitor for the p-glycoprotein transporter. The pharmacokinetics of AMPYRA are unlikely to be affected by drugs that inhibit the p-glycoprotein transporter, and dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of the p-glycoprotein transporter.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis: Two year dietary carcinogenicity studies of dalfampridine were conducted in mice and rats. In mice, the doses tested (approximately 2, 12.5, and 80 mg/kg/day) were associated with plasma exposures (AUC) up to 18 times the plasma AUC in humans at the maximum recommended human dose (MRHD) of 20 mg/day. There was no evidence of drug-related carcinogenicity.

In rats, the doses tested (approximately 2, 6, and 18 mg/kg/day) were approximately 1, 3, and 9 times the MRHD on a body surface area (mg/m^2) basis. There was a significant increase in uterine polyps at the highest dose tested.

Mutagenesis: Dalfampridine was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma *tk*, chromosomal aberration) and *in vivo (*mouse bone marrow, rat erythrocyte micronucleus) genetic toxicology assays.

Impairment of Fertility: Oral administration of dalfampridine (doses of 1, 3, and 9 mg/kg/day) to male and female rats prior to and throughout mating, and continuing in females up to day 13 of gestation or day 21 of lactation resulted in no adverse effects on fertility. Reduced offspring viability and body weight were observed at 9 mg/kg/day. The mid dose (a no-effect dose) was similar to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

The effectiveness of AMPYRA in improving walking in patients with multiple sclerosis was evaluated in two adequate and well controlled trials involving 540 patients. Patients in these two clinical trials had a mean disease duration of 13 years and a mean Kurtzke Expanded Disability Status Scale (EDSS) score of 6.

Trial 1 was a randomized, placebo-controlled, parallel group, 21-week study (one week post screening, two-week, single-blind placebo run-in, 14-week double-blind treatment, and 4-week no treatment follow-up) in 301 patients with multiple sclerosis at 33 centers in the U.S. and Canada: 229 patients assigned to AMPYRA 10 mg twice daily and 72 patients assigned to placebo. A total of 283 patients (212 AMPYRA and 71 placebo) completed all study visits. Patient inclusion criteria included the ability to walk 25 feet in 8–45 seconds. Patient exclusion criteria included a history of seizures or evidence of epileptiform activity on a screening EEG, and onset of an MS exacerbation within 60 days.

Trial 2 was a randomized, placebo-controlled, parallel group, 14-week study (one week post-screening, two weeks of single-blind, placebo run-in, nine weeks of double-blind treatment, and two weeks of no-treatment follow-up) in 239 patients with multiple sclerosis at 39 centers in the U.S. and Canada: 120 patients assigned to 10 mg twice daily and 119 assigned to placebo. A total of 227 patients (113 AMPYRA and 114 placebo) completed all study visits. The patient inclusion and exclusion criteria used in Trial 1 were employed in Trial 2, and in addition patients with severe renal impairment were also excluded.

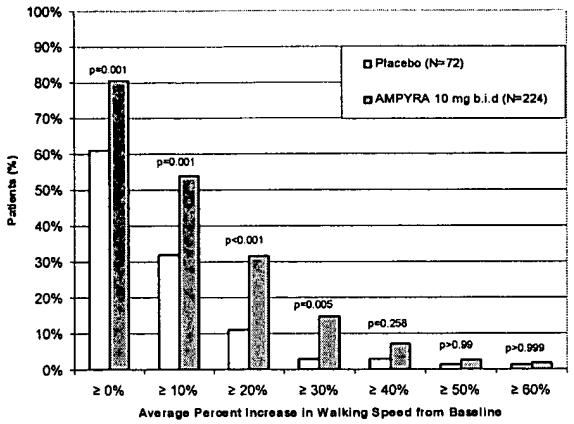
The primary measure of efficacy in both trials was walking speed (in feet per second) as measured by the Timed 25-foot Walk (T25W), using a responder analysis. A responder was defined as a patient who showed faster walking speed for a least three visits out of a possible four during the double-blind period than the maximum value achieved in the five non-double-blind no treatment visits (four before the double-blind period and one after).

A significantly greater proportion of patients taking AMPYRA 10 mg twice daily were responders, compared to patients taking placebo, as measured by the T25FW (Trial 1: 34.8% vs. 8.3%; Trial 2: 42.9% vs. 9.3%). The increased response rate in the AMPYRA group was observed across all four major types of MS disease course.

During the double-blind treatment period, a significantly greater proportion of patients taking AMPYRA 10 mg twice daily had increases in walking speed

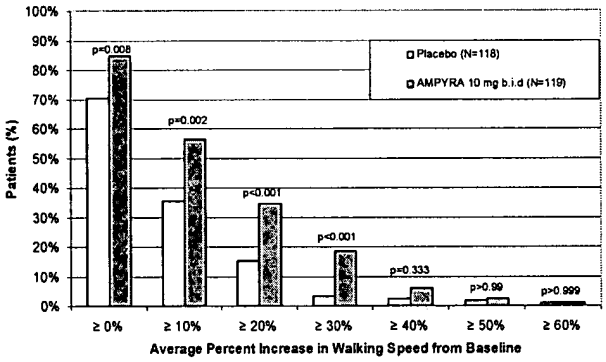
of at least 10%, 20%, or 30% from baseline, compared to placebo (Figure 1 and Figure 2).

Figure 1: Average walking speed change (%) from baseline during the double-blind phase of Trial 1



P values provided at each threshold comparing AMPYRA to placebo

Figure 2: Average walking speed change (%) from baseline during the double-blind phase of Trial 2



P values provided at each threshold comparing AMPYRA to placebo.

In Trial 1 and Trial 2, consistent improvements in walking speed were shown to be associated with improvements on a patient self-assessment of ambulatory disability, the 12-item Multiple Sclerosis Walking Scale (MSWS-12), for both drug and placebo treated patients. However, a drug-placebo difference was not established for that outcome measure.

The majority of patients in these trials (63%) were using immunomodulatory drugs (interferons, glatiramer acetate, or natalizumab), but the magnitude of improvement in walking ability was independent of concomitant treatment with these drugs. No differences in effectiveness based on degree of impairment, age, gender, or body mass index were detected. There were too few non-Caucasians in the patient population to evaluate the effect of race.

16 HOW SUPPLIED/STORAGE AND HANDLING

AMPYRA (dalfampridine) extended release tablets, 10 mg are a film-coated, white to off-white, biconvex, oval shaped, non-scored tablets with flat edge. The tablets are identified by a debossed code "A10" on one side and are available in bottles of 60.

- NDC 10144-427-60 bottles of 60 tablets

Store at 25°C (77°F). Excursions permitted 15–30°C (59–86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Risk of Seizures

Inform patients that AMPYRA causes seizures in a dose-dependent fashion, and that they must discontinue use of AMPYRA if they experience a seizure.

17.2 AMPYRA dosing

Instruct patients to take AMPYRA exactly as prescribed. Instruct patients not to take a double dose after they miss a dose. Instruct patients not take more than 2 tablets in a 24-hour period and to make sure that there is an approximate 12-hour interval between doses.

17.3 Storage

Advise patients to store AMPYRA at 25°C (77°F), with excursions permitted to 15–30°C (59–86°F). Advise patients to safely throw away AMPYRA that is out of date or no longer needed.

MEDICATION GUIDE FOR
AMPYRA™ (am-PEER-ah)
(dalfampridine) Extended Release Tablets
Read this Medication Guide before you start taking AMPYRA.

Read this Medication Guide before you start taking AMPYRA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about AMPYRA?
AMPYRA can cause seizures.

- Your chance of having a seizure is higher if you take too much AMPYRA or if you have kidney problems.
- Do not take AMPYRA if you have ever had a seizure.
- Before taking AMPYRA tell your doctor if you have kidney problems.
- Take AMPYRA exactly as prescribed by your doctor. See "How do I take AMPYRA?"

Stop taking AMPYRA and call your doctor right away if you have a seizure while taking AMPYRA.

What is AMPYRA?
AMPYRA is a prescription medicine used to help improve walking in people with multiple sclerosis (MS). This was shown by an increase in walking speed.
It is not known if AMPYRA is safe or effective in children less than 18 years of age.

Who should not take AMPYRA?
Do not take AMPYRA if you:

- have ever had a seizure
- have certain types of kidney problems

What should I tell my doctor before taking AMPYRA?
Before you take AMPYRA, tell your doctor if you:

- have any other medical conditions
- are taking compounded 4-aminopyridine (fampridine, 4-AP)
- are pregnant or plan to become pregnant. It is not known if AMPYRA will harm your unborn baby. You and your doctor will decide if you should take AMPYRA while you are pregnant
- are breast-feeding or plan to breast-feed. It is not known if AMPYRA passes into your breast milk. You and your doctor should decide if you will take AMPYRA or breast-feed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.
Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take AMPYRA?

- Take AMPYRA exactly as your doctor tells you to take it. Do not change your dose of AMPYRA.
- Take one tablet of AMPYRA 2 times each day about 12 hours apart. Do not take more than 2 tablets of AMPYRA in a 24-hour period.
- Take AMPYRA tablets whole. Do not break, crush, chew or dissolve AMPYRA tablets before swallowing. If you cannot swallow AMPYRA tablets whole, tell your doctor.
- AMPYRA is released slowly over time. If the tablet is broken, the medicine may be released too fast. This can raise your chance of having a seizure.
- AMPYRA can be taken with or without food.
- If you miss a dose of AMPYRA, do not make up the missed dose. Do not take 2 doses at the same time. Take your next dose at your regular scheduled time.
- If you take too much AMPYRA, call your doctor or go to the nearest hospital emergency room right away.
- Do not take AMPYRA together with other aminopyridine medications, including compounded 4-AP (sometimes called 4-aminopyridine, fampridine).

What are the possible side effects of AMPYRA?
AMPYRA may cause serious side effects, including:

- Kidney or bladder infections

See "What is the most important information I should know about AMPYRA?"

The most common side effects of AMPYRA include:

- urinary tract infection
- trouble sleeping (insomnia)
- dizziness
- headache
- nausea
- weakness
- back pain
- problems with balance
- multiple sclerosis relapse
- burning, tingling or itching of your skin
- irritation in your nose and throat

- constipation
- indigestion
- pain in your throat

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of AMPYRA. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store AMPYRA?

- Store AMPYRA at 59°F to 86°F (15°C to 30°C).
- Safely throw away AMPYRA that is out of date or no longer needed.

Keep AMPYRA and all medicines out of the reach of children.

General Information about the safe and effective use of AMPYRA
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMPYRA for a condition for which it was not prescribed. Do not give AMPYRA to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about AMPYRA. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AMPYRA that is written for health professionals.
For more information, go to www.AMPYRA.com or call 1-800-367-5109.

What are the ingredients in AMPYRA?
Active ingredient: dalfampridine (previously called fampridine)
Inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Distributed by: Acorda Therapeutics, Inc.
Hawthorne, NY 10532

Issued 01/2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA APPROVAL

NDA 022250

Acorda Therapeutics, Inc.
Attention: Brian A. Walter, Ph.D.
Senior Director, Regulatory Affairs
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

Please refer to your new drug application (NDA) dated April 22, 2009, received April 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AMPYRA (dalfampridine) Extended Release Tablets.

We also acknowledge receipt of the following amendments and correspondence dated:

May 8, 2009	August 5, 2009	November 23, 2009
May 15, 2009	August 12, 2009	November 25, 2009
May 20, 2009	August 14, 2009	December 2, 2009
May 28, 2009	August 20, 2009	December 8, 2009
June 22, 2009	September 4, 2009	December 15, 2009 (3)
June 24, 2009	September 8, 2009	December 29, 2009
June 30, 2009	September 14, 2009	January 6, 2010 (2)
July 14, 2009	September 16, 2009 (2)	January 8, 2010
July 21, 2009	September 18, 2009	January 14, 2010
July 22, 2009	September 21, 2009 (2)	January 19, 2010 (4)
July 24, 2009	October 20, 2009	January 20, 2010 (2)
August 4, 2009	October 28, 2009	January 21, 2010

This new drug application provides for the use of AMPYRA (dalfampridine) to improve walking, as demonstrated in walking speed, in individuals with multiple sclerosis (MS).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission, "**SPL for approved NDA 022250**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the draft carton and immediate container labels submitted on January 6, 2010 as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled
Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).
Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022250.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for AMPYRA (dalfampridine) to ensure the benefits of the drug outweigh the risk of seizures.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that AMPYRA (dalfampridine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of AMPYRA (dalfampridine). FDA has determined that AMPYRA (dalfampridine) is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use, or continue to use AMPYRA (dalfampridine). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed AMPYRA (dalfampridine).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on January 15, 2010 and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. A summary of all reported seizures with analysis of adverse event reporting by prescriber type
b. An evaluation of healthcare providers' (HCPs) understanding and patients' understanding of the serious risks of AMPYRA (dalfampridine)
    - The survey instruments and methodologies will be provided to FDA for review and comment at least 3 months before it is administered to patients and prescribers.
c. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that provider awareness is not adequate.
d. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
e. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
f. Based on the information submitted, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

We request that you submit all adverse reports of seizures as expedited reports.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022250
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022250
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 022250
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the following potential serious risks: the potential for the impurity, (b)(4), to adversely affect embryo-fetal development, the abuse potential of dalfampridine, or the potential of genotoxicity related to the impurity, (b)(4).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR 1582-1:

Embryo-fetal development study in one non clinical species (the rat) to qualify (b)(4), a drug product impurity with a specification limit that

exceeds the qualification threshold. This study may be conducted on dalfampridine spiked with the impurity up to a level that provides a safety margin compared to the specification limit proposed, and include a group receiving a high dose of dalfampridine alone. The timetable you submitted on January 21, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by January 1, 2011
Study Completion Date:	by July 1, 2011
Final Report Submission:	by January 1, 2012

PMR 1582-2:

An in vitro bacterial mutagenicity (Ames) assay for impurity, [redacted]$^{(b)(4)}$, (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the [redacted]$^{(b)(4)}$ in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the [redacted]$^{(b)(4)}$ in the drug product, then the [redacted]$^{(b)(4)}$ would be considered qualified and the genetic toxicology study would not be needed. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by July 28, 2010
Study Completion Date:	by April 25, 2011
Final Report Submission:	by August 23, 2011

PMR 1582-3:

In vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay for the impurity, [redacted]$^{(b)(4)}$, (tested directly) that has been identified as a potentially genotoxic impurity based on SAR. If data can be provided to document that plasma exposure (AUC) to the [redacted]$^{(b)(4)}$ in mouse or rat provides an adequate margin (≥25-fold) above the presumed plasma exposure in humans resulting from the presence of the [redacted]$^{(b)(4)}$ in the drug product, then the [redacted]$^{(b)(4)}$ would be considered qualified and the genetic toxicology study would not be needed. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	by July 28, 2010
Study Completion Date:	by April 25, 2011
Final Report Submission:	by August 23, 2011

PMR 1582-4:

A non-clinical self-administration study to assess the abuse potential of dalfampridine. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by April 1, 2011
Final Report Submission: by June 1, 2011

PMR 1582-5:

A receptor binding study (dopamine, serotonin, GABA [gamma-amino-butyric-acid], opioid, NMDA, monoamine, sodium channel, calcium channel, and cannabinoid receptor sites) to assess the abuse potential of dalfampridine. The timetable you submitted on January 14, 2010 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by November 1, 2010
Final Report Submission: by January 1, 2011

PMR 1582-6:

Assessment of adverse events related to abuse potential from clinical studies and clinical trials. MedDRA terms that report incidents of euphoria-related behaviors should be emphasized: impaired attention, cognition, mood, and psychomotor events; and dissociative or psychotic behaviors (see below). Complete case report forms (CRF) should be provided for any individual who experiences overdose or psychiatric or neurological adverse events during a Phase 1, 2 or 3 study or clinical trial. A compilation of abuse-related adverse events terms, which is based on our experience to date, is included in Appendix 2 of this letter.

The timetable you submitted on December 19, 2009 states that you will conduct this study according to the following schedule:

Final Protocol Submission: by April 1, 2010
Study Completion Date: by January 1, 2011
Final Report Submission: by April 1, 2011

Submit the protocols to your IND, with a cross-reference letter to this NDA . Submit all final reports to NDA 022250. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO THE REPORTING REQUIREMENTS OF SECTION 506B

We remind you of your postmarketing commitments in your submissions dated January 19 & 20, 2010. These commitments are listed below.

PMC 1582-7:

A randomized prospective placebo controlled trial to evaluate the efficacy of dalfampridine SR 5 mg twice daily in patients with multiple sclerosis; the trial should include a 10 mg twice daily arm. The primary outcome measure should be the improvement in walking speed as measured by the Timed 25-Foot Walk during the treatment period of 4 weeks. The trial should not exclude patients with EEG abnormalities who do not have a history of seizures. The trial should incorporate testing to assess the risk for urinary tract infections. The trial should be submitted to the FDA for special protocol assessment.

Final Protocol Submission:	by May 1, 2010
Trial Completion date:	by November 1, 2012
Final Report Submission:	by March 1, 2013

PMC 1582-8:

Support the addition of a7.5 mg dosage strength, for use in patients with mild or moderate renal impairment, a population at risk for drug accumulation. Such support may include an evaluation of the pharmacokinetics of the 7.5 mg dose. The proposal should be submitted to the Division for comment prior to study initiation.

Final Protocol Submission:	by May 1, 2010
Study Completion date:	by September 1, 2011
Final Report Submission:	by December 1, 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for studies or clinical trials, the number of patients entered into each study or trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

CHEMISTRY, MANUFACTURING AND CONTROLS

A shelf-life of 36 months is granted for AMPYRA (dalfampridine) Tablets packaged in 60-count, 60 cc HDPE round bottles, and physician samples packaged in 14-count in 30 cc HDPE round bottles.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05

5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). Please note that any seizure case and any serious liver injury case must be submitted as 15-day reports. We also request that assessment of adverse events related to abuse potential be compiled in PSURs with an emphasis on MedDRA terms that report incidents of euphoria-related behaviors; impaired attention, cognition, mood, and psychomotor events; and dissociative or psychotic behaviors (see below).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at
http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Hamet Touré, PharmD, Regulatory Health Project Manager, at 301-796-7534.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures
Appendix 1: Content of Labeling (Package Insert, MedGuide)
Appendix 2: Abuse-Related Adverse Event Terms
Appendix 3: REMS

Appendix 2 Abuse-Related Adverse Event Terms

The list below is a compilation of abuse-related adverse events terms, based on our experience to date. The list includes specific terms that are in the MedDRA dictionary and frequently used verbatim terms, words or phrases. Most terms are listed under General, Neurological, and Psychiatric Disorders High Level Groupings.

The presence of euphoria or other positive mood changes is a key observation that may influence a recommendation for scheduling. However, the overall behavioral profile and pharmacologic similarity to a scheduled drug is critical in determining whether scheduling will be recommended, and if so, into which schedule the drug will be recommended for placement.

Euphoria-related terms:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood: mood elevated, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.

Feeling of relaxation: feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination: (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laugher, inappropriate mood elevation.

Terms indicative of impaired attention, cognition, mood, and psychomotor events:

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances: mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder,

emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

Dissociative/psychotic terms:

Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia.

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
01/22/2010

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United States Patent and Trademark Office

Patent Bibliographic Data				02/23/2010 09:22 PM	
Patent Number:	5540938		**Application Number:**	08328165	
Issue Date:	07/30/1996		**Filing Date:**	10/24/1994	
Title:	FORMULATIONS AND THEIR USE IN THE TREATMENT OF NEUROLOGICAL DISEASES				
Status:	4th, 8th and 12th year fees paid			**Entity:**	Large
Window Opens:	N/A	**Surcharge Date:**	N/A	**Expiration:**	N/A
Fee Amt Due:	Window not open	**Surchg Amt Due:**	Window not open	**Total Amt Due:**	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	02/04/2008 01/30/2008 01/30/2004 01/28/2000	Maintenance Fee Reminder Mailed. Payment of Maintenance Fee, 12th Year, Large Entity. Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	MARLA J CHURCH ELAN PHARMACEUTICAL RESEARCH CORP 1300 GOULD DR GAINESVILLE, GA 30504				

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MARLA J CHURCH
ELAN PHARMACEUTICAL RESEARCH CORP
1300 GOULD DR
GAINESVILLE GA 30504

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,540,938	**$830.00**	**$0.00**	**01/28/00**	**08/328,165**	**07/30/96**	**10/24/94**	**04**	**NO**	**93.1806C.US**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,540,938	**$2,090.00**	**$0.00**	**01/30/04**	**08/328,165**	**07/30/96**	**10/24/94**	**08**	**NO**	**93.1806C.US**

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GAINESVILLE GA 30504

MAINTENANCE FEE STATEMENT

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The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,540,938	**$3,910.00**	**$0.00**	**01/30/08**	**08/328,165**	**07/30/96**	**10/24/94**	**12**	**NO**	**93.1806C.US**

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved
OMB No. 57-R0030

9

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION FOR A NEW DRUG

Name of Sponsor: Floyd A. Davis, M. D.

Address: Rush-Presbyterian-St. Luke's Medical Center, 1753 W. Congress Pkwy, Chicago, 60612

Date: 11.25.79

Name of Investigational Drug: 4-Aminopyridine

To the Secretary of Health, Education and Welfare
For the Commissioner of Food and Drugs
Bureau of Drugs (HFD-106)
5600 Fishers Lane
Rockville, Maryland 20852

Dear Sir:

The sponsor, Floyd A. Davis, M. D., submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and §312.1 of Title 21 of the Code of Federal Regulations.

Attached hereto in triplicate are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of, any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

d. If the drug is a radioactive drug, sufficient data must be available from animal studies or previous human studies to allow a reasonable calculation of radiation absorbed dose upon administration to a human being.

7. A total (one in each of the three copies of the notice) of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested

prior investigations and experience with the drug under investigation and related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the nature of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in section 10 of the "Notice of Claimed Investigational Exemption for a New Drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD-1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations and a description of the institutional review committee, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies. If a drug is a radioactive drug, the clinical pharmacology phase must include studies which will obtain sufficient data for dosimetry calculations. These studies should evaluate the excretion, whole body retention, and organ distribution of the radioactive material.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

c. Institutional review committee. If the phase of clinical study as described under 10a and b above are conducted on institutionalized subjects or are conducted by an individual affiliated with an institution which agrees to assume responsibility for the study, assurance must be given that an institutional review committee is responsible for initial and continuing review and approval of the proposed clinical study. The membership must be comprised of sufficient members of varying background, that is, lawyers, clergymen, or laymen as well as scientists, to assure complete and adequate review of the research project. The membership must possess not only broad competence to comprehend the nature of the project, but also other competencies necessary to judge the acceptability of the project or activity in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. Assurance must be presented that neither the sponsor nor the investigator has participated in selection of committee members; that the review committee does not allow participation in its review and conclusions by any individual involved in the conduct of the research activity under review (except to provide information to the committee); that the investigator will report to the committee for review any emergent problems, serious adverse reactions, or proposed procedural changes which may affect the status of the investigation and that no such change will be made without committee approval except where necessary to eliminate apparent immediate hazards; that reviews of the study will be conducted by the review committee at intervals appropriate to the degree of risk, but not exceeding 1 year, to assure that the research project is being conducted in compliance with the committee's understanding and recommendations; that the review committee is provided all the information on the research project necessary for its complete review of the project; and that the review committee maintains adequate documentation of its activities and develops adequate procedures for reporting its findings to the institution. The documents maintained by the committee are to include the names and qualifications of committee members, records of information provided to subjects in obtaining informed consent, committee discussion on substantive issues and their resolution, committee recommendations, and dated reports of successive reviews as they are performed. Copies of all documents are to be retained for a period of 3 years past the completion or discontinuance of the study and are to be made available upon request to duly authorized representatives of the Food and Drug Administration. (Favorable recommendations by the committee are subject to further appropriate review and rejection by institution officials. Unfavorable recommendations, restrictions, or conditions may not be overruled by the institution officials.) Procedures for the organization and operation of institutional review committees are contained in guidelines issued pursuant to Chapter 1-40 of the Grants Administration Manual of the U.S. Department of Health, Education, and Welfare, available from the U.S. Government Printing Office. It is recommended that these guidelines be followed in establishing institutional review committees and that the committees function according to the procedures described therein. A signing of the Form FD-1571 will be regarded as providing the above necessary assurances. If the institution, however, has on file with the Department of Health, Education, and Welfare, Division of Research Grants, National Institutes of Health, an "accepted general assurance," and the same committee is to review the proposed study using the same

statement to this effect should be provided with the signed FD-1571. (In addiuon to sponsor's continuing responsibility to monitor the study, the Food and Drug Administration will undertake investigations in institutions periodically to determine whether the committees are operating in accord with the assurances given by the sponsor.)

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or plan is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed,

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the commercialization of a new drug for which an application is not approved.

14. A statement that the sponsor assures that clinical studies in humans will not be initiated prior to 30 days after the date of receipt of the notice by the Food and Drug Administration and that he will continue to withold or to restrict clinical studies if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days. If such request is made, the sponsor will be provided specific information as to the deficiencies and will be afforded a conference on request. The 30-day delay may be waived by the Food and Drug Administration upon a showing of good reason for such waiver; and for investigations subject to institutional review committee approval as described in item 10c above, an additional statement assuring that the investigation will not be initiated prior to approval of the study by such committee.

15. When requested by the agency, an environmental impact analysis report pursuant to § 6.1 of this chapter.

Very truly yours,

Floyd A. Davis, M. D.

SPONSOR	PER
	INDICATE AUTHORITY

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

ALL NOTICES AND CORRESPONDENCE SHOULD BE SUBMITTED IN TRIPLICATE.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-250

NDA ACKNOWLEDGMENT

Acorda Therapeutics, Inc.
Attention: Brian A. Walter, Ph.D.
Senior Director, Regulatory Affairs
15 Skyline Drive
Hawthorne, NY 10532

Dear Dr. Walter:

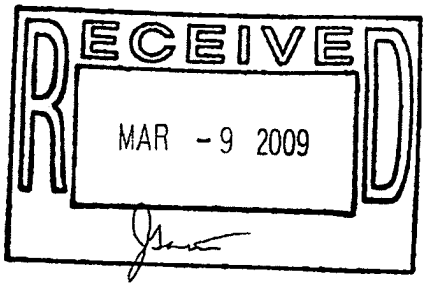
We have received your new drug application (NDA) submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Fampridine-SR Tablets

Date of Application: January 30, 2009

Date of Receipt: January 30, 2009

Our Reference Number: NDA 22-250



Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 31, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call James H. Reese, PhD, RAC, Regulatory Project Manager, at (301) 796-1136.

Sincerely,

{See appended electronic signature page}

James H. Reese, PhD, RAC
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James Reese
2/19/2009 03:05:55 PM

DEPARTMENT OF
HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation Research
5901–B Ammendale Road
Beltsville, MD 20705–1266

DR1

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
1979			
11/23/79	IND Request	FDA FORM 157 Statement of investor [FDA Form 1571 (11/75)]	Notice of Claimed Investigational Exemption for a New Drug
1986			
12/22/86	Full Submission	Orphan Drug Designation Request	Orphan Drug Designation Request
1987			
1/15/1987	Full Submission	Amendment	Amendment to 12/22/86 Submission
2/14/1987		Amendment	Amendment to 12/22/86 Submission
06/2/87	FDA Letter	FDA Approval Letter	Official Notification of Orphan Drug Designation
1988			
3/1/88	Full Submission	Gen Cor	Treatment IND Treatment Protocol
1990			
12/20/90	Full Submission	Gen Cor	Acceptance of Sponsorship
1991			
7/26/91		Gen Cor	Copy of Original IND Request
9/23/91	Full Submission	Clinical Protocol	Clin Protocol # 1091-001
10/30/91	Full Submission	Gen Cor	Info Amendment
11/11/91	Full Submission	IND Safety Report	Safety
11/13/91	Full Submission	Study Report	Final Clin Study Reports (Final Toxicity Study)
1992			
1/7/92	FDA Letter	Annual report	Annual Report
1/17/92	FDA Letter	Gen Cor	Acknowledgment of receipt PK/PD comments & recommendation
1/31/92	Full Submission	Gen Cor	PK/PD
2/3/92	Full Submission	Annual report	Annual Report
3/18/92	Draft Clin Prot	Draft Clin Prot	Draft Clin Prot # 92-03-02

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
3/24/92	Letter to FDA	Formal Request	Written Formal request
5/1/92	Full Submission	Final Pre clinical study reports	Final Pre clinical study reports
5/6/92	Full Submission	Agenda Proposal	Pre meeting Package (1979 to Present)
5/13/92	Letter	Response to FDA Request	Response to FDA Request
5/18/92	Full Submission	Gen Cor	Meeting Confirmation
6/2/92	Full Submission	Gen Cor	Clinical
6/12/92	FDA Letter	Gen Cor	Meeting minutes
6/22/92	Fax to FDA	Fax	Fax to FDA
6/23/92	Full Submission	Gen Cor	Meeting Minutes
6/30/92	Full Submission	Gen Cor	Meeting Follow Up Package
7/8/92	Full Submission	Gen Cor	Minutes of Meeting
7/17/92	Full Submission	Gen Cor	Minutes of a phone conversation
8/28/92	Full Submission	Preclinical Protocols	Preclinical Protocols
10/30/92	Full Submission	Gen Cor	IND Safety Report
11/3/92	Letter from FDA	Copy of FDA Minutes and recommendations	FDA Minutes of 6/23/92 and recommendations
11/3/92	Letter from FDA	Copy of FDA Minutes and recommendations	FDA Minutes of 6/23/92 and recommendations
11/3/92	FDA Letter	FDA Min of Meeting 6/23/92 and FDA comments	Protocol Amend
1993			
1/13/93	Full Submission	Gen Cor	Protocol Amend
2/23/93	Full Submission	Gen Cor	Clin and Chem Info
3/11/93	FDA Letter	FDA Letter	FDA Authorization
4/6/93	Full Submission	Gen Cor	Clin Tox
4/21/93	Full Submission	Gen Cor	Clin
4/27/93	Full Submission	Gen Cor	CMC
5/11/93	Full Submission	Gen Cor	AE CMC
6/2/93	Full Submission	Gen Cor	IND Safety Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
6/10/93	File	CMC Batch Record	4-AP Injection 10 mg/ml Vial CBL Lot# 28401 Elan Lot # 4AP9301
8/31/93	Full Submission	Gen Cor	IND Safety Report
10/26/93	Full Submission	Gen Cor	Clin CMC
11/24/93	Full Submission	Gen Cor	Prot Amend
11/30/93	FDA Letter	Gen Cor	Annual Report
12/8/93	Full Submission	Gen Cor	IND Safety Report
12/20/93	Full Submission	Gen Cor	IND Safety Report
1994			
1/7/94	Full Submission	Gen Cor	Annual Report. Final Pre Clin Rep
2/4/94	Full Submission	Gen Cor	Clin Prot, CMC
3/18/94	Full Submission	Gen Cor	CMC Amend
5/19/94	Full Submission	Gen Cor	IND Safety Report
6/23/94	Full Submission	Gen Cor	CMC Amend
8/5/94	Full Submission	Gen Cor	Clin Prot New Protocol New Investigator 0494-001us
8/19/94	Full Submission	Gen Cor	Clin Prot Amend Change in Protocol and New Investigator
8/26/94	FDA Letter	Gen Cor	Clin Prot Amend
9/15/94	Full Submission	Gen Cor	CMC Amend
9/27/94	Full Submission	Gen Cor	IND Safety Report
10/12/94	Full Submission	Gen Cor	Clin
10/19/94	Full Submission	Gen Cor	IND Safety Report
10/31/94	Full Submission	Gen Cor	IND Safety Report
12/5/94	Full Submission	Gen Cor	Clin
12/6/94	Full Submission	Gen Cor	IND Safety Report
12/8/94	Full Submission	Gen Cor	IND Safety Report
12/12/94	Full Submission	Gen Cor	IND Safety Report
12/21/94	Full Submission	Gen Cor	IND Safety Report
12/23/94	Full Submission	Gen Cor	IND Safety Report
1995			
1/9/95	Full Submission	Gen Cor	Clin 0494-001us
1/16/95	Full Submission	Gen Cor	IND Safety Report
1/19/95	Full Submission	Gen Cor	Clin

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
1/19/95	Full Submission	Gen Cor	Annual Report Orphan Drug
1/25/95	Full Submission	Gen Cor	IND Safety Report
1/25/95	Full Submission	Gen Cor	Clin 0494-001us
2/6/95	Letter from FDA	FDA Comment & recommendations	Study No. 0494-001US
2/16/95	Full Submission	Gen Cor	CMC
3/8/95	Full Submission	Gen Cor	Clin
3/21/95	Full Submission	Gen Cor	IND Safety Report
3/29/95	Full Submission	Gen Cor	Annual Report
5/8/95	Full Submission	Gen Cor	IND Safety Report
5/17/95	Full Submission	Gen Cor	Protocols for Carcinogenicity Study
5/31/95	Full Submission	Gen Cor	Amendment IV to Protocol
6/20/95	Full Submission	Gen Cor	Amendment to Protocol
7/11/95	Telecon	Telecon	Outstanding Toxicology requests and further clarification
7/26/95	Full Submission	Gen Cor	IND Safety Report
7/27/95	Full Submission	Gen Cor	Amendment to Protocol
08/10/95	Full Submission	Gen Cor	IND Safety Report
9/7/95	Full Submission	Gen Cor	New Phase I Protocol and Investigator Info.
9/14/95	Full Submission	Gen Cor	Prot Amendment Change in Protocol
10/5/95	Full Submission	Gen Cor	IND Safety Report
11/30/95	Full Submission	Gen Cor	IND Safety Report
12/6/95	Full Submission	Gen Cor	IND Safety Report
12/22/95	Full Submission	Gen Cor	IND Safety Report
1996			
1/23/96	Full Submission	Gen Cor	IND Safety Report
2/12/96	Full Submission	Gen Cor	IND Safety Report
3/5/96	Full Submission	Gen Cor	IND Safety Report
3/22/96	Full Submission	Gen Cor	Annual Report
3/28/96	Full Submission	New Protocol	New Phase 1 Prot. 0296-002US

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627			
DATE	MEDIA	TYPE	SUBJECT
5/21/96	Full Submission	Gen Cor & IND Safety Reports	IND Safety Report & Name change of CRO
7/1/96	Full Submission	IND Safety Reports	IND Safety Report
9/6/96	Full Submission	Gen Cor	Meeting Request
10/24/96	Full Submission	Gen Cor	Meeting Correspondences
9/17/96	Nat'l Institute of Health's Approval Letter	Nat'l Institute of Health's Approval Letter	1 R43 HD34345-01A1 Single Project Assurance S-13440-01 NIH Approval
12/18/96	Full Submission	Gen Cor	Info. Amendment Pharmacology/Tox
12/23/96	Full Submission	Gen Cor	Info. Amendment Pharmacology/Tox
1997			
3/25/97	Full Submission	Gen Cor	Annual Report
5/8/97	Full Submission	Gen Cor	Final Clinical reports 0494-001us
6/24/97	Full Submission	Gen Cor	Transfer of Ownership
6/24/97	Full Submission	Gen Cor	Transfer of IND Ownership
7/1/97	Full Submission	Gen Cor	Transfer of Ownership of Orphan Drug Designation # 86-181
7/14/97	Full Submission	Gen Cor	Authorization Letter
7/14/97	FDA Letter	Gen Cor	Authorization Letter
7/29/97	Documentation	CMC Dossier	CMC Amendment for Fampridine
9/8/97	Full Submission	Gen Cor	Info Amend: CMC Clinical
10/3/97	Full Submission	Gen Cor	Change in Prot: New Prot; New Inv; Inv Brochure
1998			
1/6/98	Full Submission	Gen Cor	Prot Amend.: Change in Prot
1/21/98	Fax	Fax	Stability Protocol
3/4/98	FDA Letter	Gen Cor	FDA Comments and Requests Re: SCI-200
4/3/98	Memo	Memo	IND Annual Report Update
4/10/98	Fax	Fax	Annual Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
4/21/98	Full Submission	Gen Cor	Annual Report
4/23/98	Fax	Fax	Fax CMC Fampridine Stability Studies
6/15/98	FDA Letter	Gen Cor	FDA Approval Letter
6/17/98	Full Submission	Gen Cor	Transfer of Ownership
6/17/1998	Full Submission	Gen Cor	Transfer of Ownership
6/17/1998	Full Submission	Gen Cor	Transfer of Ownership
6/17/1998	Full Submission	Gen Cor	Transfer of Ownership
6/25/98	Full Submission	Gen Cor	IND Safety Report
8/6/98	FDA Letter to Ivah	Gen Cor	Transfer or Changes in ownership or sponsorship
8/10/98	FDA Fax to Athena	FDA Approval Letter	Orphan Drug Designation
8/17/98	Full Submission	Gen Cor	IND Safety Report
9/1/98	Full Submission	Gen Cor	Orphan Drug Designation
9/16/98	Full Submission	Gen Cor	Acknowledgement of receipt
9/21/98	Full Submission	Tel Con	FDA Request for Information
9/30/98	Full Submission	Gen Cor	Extension Request for IND Info.
11/20/98	Full Submission	Gen Cor	Response to FDA Request for Info
1999			
Form: 3/24/98 Letter: 3/25/99	Full Submission	Gen Cor	Info Amend: CMC Clinical
4/6/99	Full Submission	Gen Cor	Pre Clin Info Amend: Pharm Tox
4/7/99	Full Submission	Gen Cor	Non clinical Info Amend.
4/12/99	Full Submission	Gen Cor	Non clinical Info Amend.
4/21/99	Full Submission	Gen Cor	Annual Report
8/7/99	Full Submission	Gen Cor	Request for Meeting Clinical
9/21/99	RACR Phone Call	RACR Phone Call	Change in Signatory/update of attendee list

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
9/22/99	Full Submission	Gen Cor	Transfer of Signatory Authority
9/22/99	Full Submission	Gen Cor	Request for Meeting Clinical
10/8/99	Full Submission	Gen Cor	List of Meeting Participants
11/17/99	Full Submission	Gen Cor	Info Amend: Clinical Final reports
11/24/99	Full Submission	Gen Cor	Info Amend: Pre Clinical Pharm/Tox
11/26/99	RACR Phone Call	Gen Cor	Tel con
12/1/99	RACR Phone Call	RACR Phone Call	FDA Request for desk copy of 11/17/99 Submission
12/3/99	Full Submission	Gen Cor	Annual Report
12/3/99	Full Submission	Gen Cor	Prot Amend New Protocol Draft
12/3/99	RACR Phone Call	RACR Phone Call	Annual Report
12/23/99	Full Submission	Gen Cor	Info Amend: Clinical
2000			
1/3/00	FDA Letter	Gen Cor	FDA Comments
3/20/00	Minutes of Meeting	Acorda's Meeting Minutes of the 3/20/00 Meeting	Acorda's Meeting Minutes of the 3/20/00 Meeting
10/12/00	Full Submission	Gen Cor	Prot Amend New Protocol Draft
2001			
1/17/01	Full Submission	Gen Cor	Prot Amend New Inv, IRB Approval CRF
3/9/01	Full Submission	Gen Cor	Prot Amend New Inv, IRB Approval CRF
3/29/01	Full Submission	Gen Cor	Response to FDA Request fro Info.
4/9/01	Full Submission	Gen Cor	IND Safety Report
6/1/01	Full Submission	Gen Cor	IND Safety Report
6/15/01	Full Submission	Gen Cor	IND Safety Report
6/26/01	FDA Fax	FDA Fax	Clinical Comment and Request for Info.
6/29/01	Full Submission	Gen Cor	Response to Clinical Comment and Request for Info.

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
9/18/01	Full Submission	Gen Cor	Prot Amend Change in Prot MS-F201
9/20/01	Full Submission	Gen Cor	Transfer of Signatory Authority
9/27/01	Full Submission	Gen Cor	CMC
10/4/01	Full Submission	Gen Cor	Prot Amend Change in Prot MS-F201
10/16/01	Full Submission	Gen Cor	MS-F200 IND Safety Initial Written Report
11/21/01	Full Submission	Gen Cor	MS-F200 Clin Report
11/29/01	Full Submission	Gen Cor	Annual Report
12/14/01	Full Submission	Gen Cor	Annual Report
2002			
1/29/02	Full Submission	Gen Cor	CMC
1/31/02	Full Submission	Gen Cor	Investigator Brochure
4/10/02	Full Submission	Gen Cor	Supplementary CMC Information - Placebo Tablets
5/22/02	Full Submission	Gen Cor	Request for Meeting
5/28/02	Full Submission	Gen Cor	FDA Fax denial of Request for Meeting
7/8/02	Full Submission	Gen Cor	Final Nonclinical Study Report
7/12/02	Full Submission	Gen Cor	Request for Teleconference
7/25/2002	Full Submission	Gen Cor	Annual Report
10/11/02	Full Submission	Gen Cor	New Protocol MS-F202 Updated Investigator's Brochure
10/25/02	Full Submission	Gen Cor	Info. Amend CMC and Update to DMF
2003			
1/22/03	Full Submission	Gen Cor	Protocol Amend: Change in Protocol
3/11/03	Full Submission	Gen Cor	Minutes of 9/4/02 meeting
3/27/03	Full Submission	Gen Cor	Response to FDA Statistical Comments

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
4/8/03	Full Submission	New Investigator	Protocol Amend: New Inv
5/16/03	Full Submission	Annual Report	IND Annual Report
5/16/03	Full Submission	Gen Cor	Info Amend CMC and Revised Packaging Configuration
6/13/03	Full Submission	Gen Cor	Log Files
7/11/03	Full Submission	Initial IND Written Report	IND Safety Report
7/29/03	Full Submission	IND Safety Report	IND Safety Report
8/18/03	Full Submission	IND Safety Report	IND Safety Report
8/25/03	Full Submission	IND Safety Report	IND Safety Report
9/4/03	Full Submission	IND Safety Report	IND Safety Report
9/19/03	Full Submission	IND Safety Report	IND Safety Report
10/1/03	Full Submission	IND Safety Report	IND Safety Report
10/1/03	Full Submission	IND Safety Report	IND Safety Report
10/10/03	Full Submission	IND Safety Report	IND Safety Report
10/30/03	Full Submission	IND Safety Report	IND Safety Report
11/24/03	Full Submission	Protocol Amendment: New Protocol	Prot Amend New Protocol MS-F202 EXT
12/16/03	Full Submission	IND Safety Report	IND Safety Report
2004			
1/30/04	Full Submission	Protocol Amendment: New and Updated Investigator Information	Study MS-F202
2/27/04	Full Submission	IND Safety Report	IND Safety Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
3/10/04	Full Submission	Protocol Amendment New Investigators	Protocol Amendment New Investigators for MS-F202 EXT
4/8/04	Full Submission	Gen Cor	Request for End of phase 2 Meeting
4/14/04	Full Submission	Annual Report	IND Annual Report
4/21/04	Full Submission	Protocol Amendment New and Updated Investigator Information for MS-F202 EXT	Protocol Amendment New and Updated Investigator Information for MS-F202 EXT
6/4/04	Full Submission		Phase 2 Meeting
6/8/04	Full Submission	Gen Cor	IND Safety Report
6/11/04	Full Submission	Gen Cor	Protocol Amendment Change in Protocol
6/18/04	Full Submission	Gen Cor	IND Safety Report
8/26/04	Fax	FDA Fax	FDAs Minutes
8/27/04	Full Submission	Gen Cor	Protocol Amendment Change in Protocol
8/31/04	Full Submission	Gen Cor	MS-F203 Protocol Synopsis Request for Telecon
10/4/04	Full Submission	Gen Cor	MS-F203 Protocol Synopsis Draft Clinical Research Protocol
10/19/04	Full Submission	Gen Cor	Prot Amend: New & Updated Investigator Information 1572
11/12/04	Full Submission	Gen Cor	IND Safety Report
11/12/04	Full Submission	Gen Cor	IND Safety Report
11/16/04	Full Submission	Gen Cor	IND Safety Report
11/29/04	Full Submission	Gen Cor	Request for Telecon
12/20/04	Minutes Telecon	Gen Cor	Minutes of Telephone Conference
12/29/04	FDA Fax	FDA Fax	MS-F203 FDA Telecon Minutes of Meeting
2005			
1/10/05	Full Submission	Gen Cor	IND Safety Report
1/10/05	Full Submission	Gen Cor	IND Safety Report
1/27/05	Full Submission	Gen Cor	IND Safety Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
3/1/05	Full Submission	Gen Cor	Request for Special Prot Assessment MS-F203
3/9/05	Full Submission	Gen Cor	Prot Amend Change in Prot
3/31/05	Full Submission	Gen Cor	FSR Clin Info
3/31/05	Full Submission	Gen Cor	FSR Clin Info
3/31/05	Full Submission	Gen Cor	FSR Clin Info
3/31/05	Full Submission	Gen Cor	FSR Clin Info
3/31/05	Full Submission	Gen Cor	Info. Amend: Pharm/Tox
3/31/05	Full Submission	Gen Cor	Info. Amend: Pharm/Tox
3/31/05	Full Submission	Gen Cor	Annual Report
4/7/05	Full Submission	Gen Cor	MS-F202 Ext
4/8/05	Telecon	Telecon	Prot MS-F203 Requested Special Protocol Assessment
4/13/05	Full Submission	Gen Cor	MS-F203
5/2/05	FDA Fax	FDA Fax	FDA's Telecon Minutes
5/13/05	Full Submission	Gen Cor	MS-F203
5/24/05	Full Submission	Gen Cor	IND Safety Report
5/24/05	Full Submission	Gen Cor	IND Safety Report
5/24/05	Full Submission	Gen Cor	IND Safety Report
5/31/05	FDA Fax	FDA Fax	Ms-F203 Clin Comments
6/10/05	Full Submission	Info Amend Clin	Clinical
7/5/05	FDA Fax	FDA Fax	Clinical Comments
7/7/05	Full Submission	Gen Cor	New Inv. Info
8/11/05	Full Submission	Gen Cor	Prot Amend New Inv. Info
8/15/05	Full Submission	Gen Cor	Annual Report
8/31/05	Full Submission	Gen Cor	Info Amend. New Protocol

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
9/13/05	Full Submission	Gen Cor	DRAFT Meeting Minutes, DSMB
9/29/05	Full Submission	Gen Cor	IND Safety Report
10/4/05	Full Submission	Gen Cor	Prot Amend Change in Prot
10/5/05	Full Submission	Correspondence	Annual Report
11/30/05	Full Submission	Gen Cor	Prot Amend New Inv
11/30/05	Full Submission	Gen Cor	Prot Amend New Inv
11/30/05	Full Submission	Gen Cor	DRAFT Meeting Minutes, DSMB
12/29/05	Full Submission	Gen Cor	Annual report
2006			
1/24/06	Full Submission	Gen Cor	IND Safety Report
1/24/06	Full Submission	Gen Cor	IND Safety Report
2/15/06	Full Submission	Gen Cor	IND Safety Report
2/16/06	Full Submission	Gen Cor	IND Safety Report
3/2/06	Full Submission	Gen Cor	IND Safety Report
3/8/06	Full Submission		IND Safety Report
3/13/06	Full Submission	Gen Cor	New Inv Info MS-F203 EXT
3/24/06	Full Submission	Gen Cor 2006_03_08	IND Safety Report
3/30/06	Full Submission	Prot Amend: Change in Prot	MS-F203 V 1.2 Dated 9/20/05
3/30/06	Full Submission	Prot Amend: New Inv.	MS-F203 EXT New Invs.: Amason, Freedman, McGowan
4/5/06	Full Submission	Gen Cor	Updated Investigator's Brochure for Fampridine SR
4/14/06	Email	Email	Acorda's Inquiry on Annual Report
4/11/06	Full Submission	Gen Cor	Annual report
4/14/06	Email	Email	Acorda's Contact Information
4/14/06	Email	Email	Acorda's Contact Information
4/17/06	Email	Email	Acorda's Inquiry on Annual Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
4/27/06	Full Submission	Gen Cor	Meeting Minutes, DSMB-DRAFT
4/27/06	Full Submission	Gen Cor	Meeting Minutes, DSMB
5/3/06	Full Submission	Prot Amend	New Investigators
5/4/06	Full Submission	IND Safety Report	IND Safety Report
5/9/06	Call to FDA	Tel Call	IND Effective Date
5/12/06	Full Submission	IND Safety Report	IND Safety Report
5/23/06	Email	Email	Acorda's Proposal to FDA Re: Annual Report
5/24/06	Letter from Health Canada	Gen Cor	Acknowledgement of notification
5/25/06	Full Submission	Gen Cor	Meeting Minutes, DSMB Follow up
5/30/06	Full Submission	Gen Cor	Meeting Minutes, DSMB Follow up
6/1/06	Full Submission	Gen Cor	SAP for MS-F203
6/14/06	Full Submission	Gen Cor	Meeting Minutes, DSMB Follow up
6/16/06	Full Submission	Prot Amend	Change in Prot with a brief description of Changes Version 1.1
6/26/06	Full Submission	Gen Cor	Annual Report
7/11/06	Full Submission	Gen Cor	Protocol Amendment
7/18/06	Full Submission	Prot Amend	New Protocol No. MS-F202_203META
7/21/06	Full Submission	Info Amendment	Clinical 2 Clinical Reports
7/26/06	Full Submission	Gen Cor	MS-F203
8/2/06	Email	Email	Acorda's Proposal on Annual Report
8/4/06	Full Submission	Gen Cor	IND Safety Report
8/4/06	Full Submission	Gen Cor	IND Safety Report
8/23/06	Full Submission	Gen Cor	Acorda's request for FDA's input
8/29/06	Full Submission	Gen Cor	IND Safety Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
8/31/06	RACR	RACR	Telecon Re: DSMB Issue
9/6/06	RACR	Email	Meta Analysis Plan No. MS-F202_203META
9/6/06	Full Submission	Prot Amendment	Meta Analysis Plan No. MS-F202_203META
9/6/06	Full Submission	Gen Cor	Database Lock MS-F203
10/10/06	Full Submission	Gen Cor	Request for type c Meeting
11/2/06	Email	RACR Email	FDA Type C Meeting
11/6/06	Full Submission	Gen Cor	Type C Meeting Briefing Package
11/9/06	Email	RACR	Elec copy of 11/7/06 cover later and MS Word copy of the meeting questions
11/15/06	RACR	RACR	Request for an e-version of Briefing Package
11/16/06	CD for FDA	CD	CD containing the e-version of Briefing Package
11/18/06			
11/21/06	Full Submission	Gen Cor	IND Safety Report
12/1/06	Full Submission	Info Amendment	Final Clinical Reports
12/1/06	Full Submission	Gen Cor	Safety MSF203E_206-025
12/4/06	RACR	RACR	Email Re: Acorda's Updated Attendees List
12/5/06	RACR	RACR	Email Re: Informing FDA of the Contact information
12/6/06	RACR	RACR	Email to FDA Re: List of FDA Attendees and follow-up on questions for the meeting
12/6/06	RACR	RACR	FDA Email Re: Informing ACORDA Re-FDA Comments to Questions Meeting 12-7-06

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
12/7 & 12/8/06	RACR	RACR	Acorda requesting FDA for comments on draft Press release
12/18/06	Full Submission	Gen Cor	IND Safety Report
12/22/06	Full Submission	Protocol Amendment: New Protocol	Original Signature Page
12/22/06	Full Submission	Protocol Amendment: New Protocol	Protocol MS-F204 and request for Special Protocol Assessment
2007			
1/2/07	Full Submission	Gen Cor	IND Safety Report
1/10/07	FDA Fac	FDA Fax	FDA's Official Minutes of Meeting
1/11/07	Telephone Call	RACR Phone call	FDA Request for Copies of SPA MS-F204
1/11/07	Sent by FedEx to J Reese	9 Review Copies of SPA MS-F204	Response to FDA's Request for copies of SPA
1/18/07	RACR	RACR	FDA information request
1/19/07	Full Submission	Info Amendment	Final Clinical Reports
1/19/07	RACR Email	Info Amendment	Final Clinical Reports
1/22/07	RACR Email	Info Amendment	Final Clinical Reports
1/26/07	RACR Email	Info Amendment	Final Clinical Reports
2/8/07	Fax Letter from FDA	FDA's Review	FDA's response to Questions-Protocol MS-F204
2/20/07	Protocol Amendment	New Investigator	MS-F203 EXT
3/5/07	Protocol Amendment	New Investigators	MS-F203
3/6/07	Protocol Amendment	Change in Protocol	MS-F204
3/6/07	Full Submission	Gen Cor	IND Safety Report
3/13/07	Full Submission	Gen Cor	IND Safety Report
3/19/07	Protocol Amendment	New Investigator	MS-F203 EXT
4/2/07	Phone message and Email	RACR Phone Message and	Clinical Information Amendment
4/6/07	Full Submission	Gen Cor	IND Safety Report
4/10/07	Protocol Amendment	New Investigator	MS-F203 EXT

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
4/26/07	Full Submission	Gen Cor	Annual report
4/26/07	Full Submission	Change in Protocol	MS-F204 Protocol Amendment
4/27/07	RACR Email to FDA	RACR Change in Protocol	MS-F204 Protocol Amendment
5/1/07	RACR Email to FDA	RACR Change in Protocol	MS-F204 Protocol Amendment
5/1/07	RACR	NOL	NOL protocol Amendment
5/1/2007	Email to FDA	protocol Amendment	MS-F204 Protocol Amendment Serial No. 242
5/2/07	Full Submission	protocol Amendment	MS-F204 Protocol Amendment
5/9-10/2007	RACR Emails to-from the FDA	protocol Amendment	MS-F204 Protocol Amendment
5/11/07	RACR Emails from the FDA	protocol Amendment	MS-F204 Protocol Amendment
5/11/07	Full Submission	Change in Protocol	MS-F202 EXT Protocol Amendment
5/11/07	Full Submission	Change in Protocol	MS-F203 EXT Protocol Amendment
5/15/07	Full Submission	protocol Amendment	MS-F204 Protocol Amendment
5/18/07	Full Submission	Gen Cor	IND Safety Report
5/18/07	Full Submission	Gen Cor	IND Safety Report
5/18/07	Full Submission	Gen Cor	IND Safety Report
5/18/2007	Email and fax to FDA	protocol Amendment	MS-F204 Protocol Amendment
5/21/2007	Fax from FDA	protocol Amendment	MS-F204 Protocol Amendment
5/21/2007	Email to FDA	protocol Amendment	MS-F204 Protocol Amendment
5/21/2007	Fax from FDA	protocol Amendment	MS-F204 Protocol Amendment
5/30/07	Full Submission	Gen Cor	IND Safety Report
5/30/07	Full Submission	Gen Cor	IND Safety Report
5/30/07	Full Submission	Gen Cor	IND Safety Report
5/30/07	Full Submission	Protocol Amendment: New	Protocol MS-F204 EXT
5/31/07	Full Submission	Protocol Amendment	MS-F204 Protocol Amendment

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
6/1/07	Full Submission	Gen Cor	TQT Protocol Review
6/4/07	RACR Email	FDA Request for Information	TQTc-F-SR001 FDA Request for Info
6/14/07	Call from FDA	FDA Request for Information	TQTc-F-SR001 FDA Request for Info
6/19/07	Full Submission	Response to FDA Request for	TQT Protocol
6/20/07	RACR Email to FDA	Email to FDA	Serial No 252 Response to FDA Request for Info
6/26/07	Full Submission	protocol Amendment	MS-F204 Protocol Amendment
7/18/07	Full Submission	protocol Amendment	MS-F204 EXT Protocol Amendment
7/18/07	Full Submission	Gen Cor	Updated Investigator's Brochure for Fampridine SR
7/20/07	RACR	RACR Tel Call	TQT Protocol
7/23/07	Email from FDA	Email from FDA	TQT Protocol
7/23-24 and 7/26/2007	RACR Emails	RACRs 3 Emails	QT Review Documents
7/27/07	Full Submission	Gen Cor	Updated Investigator's Brochure for Fampridine SR
8/1/07	Full Submission	Gen Cor	TQT Protocol
8/3 and 8/6/07	RACR Emails	RACRs Emails	QT Review Documents
8/8-9/2007	RACR Email	3 Emails RACR	Request for an IND Number (for IND 17,627)
8/8/07	Full Submission	Protocol Amendment	MS-F202 EXT Protocol Amendment
8/10/07	Full Submission	Protocol Amendment	MS-F202 EXT Protocol Amendment
8/10/07	Full Submission	Protocol	MS-F202 EXT SAP
8/15/07	RACR Call from FDA	Call from FDA	TQT Protocol
8/17/07	Full Submission	Gen Cor	Request for End of Phase 2 meeting
8/22/07	RACR email from FDA	Email from FDA	TQT Protocol Synopsis
8/30/07	Full Submission	Gen Cor	IND Safety Report
9/7/07	Full Submission	Gen Cor	Protocol Amendment: New protocol

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
9/11/07	Full Submission	Change in Protocol	MS-F204 Protocol Amendment
9/12 and 9/14/07	Email to and from FDA	RACR Email	Follow up on Pre NDA Meeting
9/14/07	Full Submission	New Investigator	MS-F203 EXT
9/17/07	Full Submission	New Investigator	MS-F202 EXT
9/17/07	Full Submission	New Investigator	MS-F204 EXT
9/20/07	Full Submission	Info Amendment	Final Clinical Reports
10/1/07	Fax from FDA	FDA Fax	Fampridine-Sir QTc Protocol
10/2/07	RACR Tel calls	RACR Call to and from FDA	Upcoming Pre-NDA Meeting Package
10/3/07	Full Submission	Gen Cor	Briefing Package Pre-NDA Type B Meeting
10/4/07	RACR Email	RACR Email	10 Sets Review Copy
10/5/07	Full Submission	Gen Cor	IND Safety Report
10/9/07	Full Submission	Gen Cor	SAP
10/11/07	Full Submission	Gen Cor	SAP for MS-F202 EXT Amendment No. 1
10/17/07	RACR	RACR Phone call	Phone call to FDA
10/17/07	RACR	RACR Phone call	Phone call to FDA
10/18/07	RACR	RACR Email from DNP/FDA	FDA's email confirmation receipt of cover letter only of Acorda's Response to FDA's comments on TQT Protocol
10/18/07	Full Submission	Gen Cor	Acorda's Response to FDA's comments on TQT Protocol
10/19/07	RACR	RACR Email to DNP/FDA	Acorda's Response to FDA's comments on TQT Protocol
10/25/07	FDA Email	RACR Email from DNP/FDA	FDA's Comments Re: Pre NDA Meeting package for 10/31/07
10/31/07	FDA Email	RACR Email from DNP/FDA	FDA's Follow Up Comments from the IRT - QT team
11/9/07	Full Submission	Protocol Amendment	MS-F204 Ext Protocol Amendment
11/13/07	Full Submission		IND Safety Report

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
11/21/07	Full Submission	Gen Cor	IND Safety Report
11/28/07	Full Submission	Gen Cor	SAP
12/3/07	Email to FDA	Gen Cor	SAP - PROTOCOL NUMBER: TQTc-F-SR001
12/4/07	Full Submission	Gen Cor	Sponsor's minutes of 10/31/07 Meeting
12/6/07	Full Submission	Protocol Amendment: New	Protocol MS-F204 EXT
12/12/07	Full Submission	Protocol Amendment: New	Protocol MS-F204 EXT
12/19/07	Full Submission	Gen Cor	IND Safety Report
12/21/07	Full Submission	Gen Cor	IND Safety Report
12/21/07	Email/RACR	Email RACR	FDA Memorandum of Meeting Minutes
12/27/07	Full Submission	Gen Cor	IND Safety Report
2008			
1/15/08	Full Submission	Gen Cor	Protocol MS-F204
1/15/08	Full Submission	Protocol Amendment	Change in Protocol
1/18/08	Full Submission	Protocol Amendment	Change in Protocol
1/18/08	Full Submission	Gen correspondence	Change in Protocol
1/22/08	Full Submission	Gen correspondence	Database Locked TQTc-F-SR001 Study
1/28/08	Full Submission	Gen correspondence	Amendment Sap MS-F202 EXT
1/29/08	Full Submission	Gen correspondence	Amendment Sap MS-F203 EXT
1/30/08	Email/RACR	Email RACR	FDA Requested a 30-min Tele Conf.
1/30/08	Full Submission	Gen correspondence	SAP ISE for MS-F201, MS-F202, MS-F203, and MS-F204
2/4/08	Email RACR	Email RACR	FDA Request for Copy of Current ICF
2/4/08	Email RACR	Email RACR	Acorda's reply to FDA Request for Copy of Current ICF

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
2/6/08	Full Submission	Gen correspondence	Type C Meeting (Telecon)
2/6/08	Full Submission	Gen correspondence	Clarification TK bridging studies
2/21/08	Full Submission	Gen Cor	IND Safety Report
2/29/08	Full Submission	Gen Cor	IND Safety Report
3/4/08	Email/RACR	Email RACR	Fampridine-SR: FDA Letter for CMC Mtg. and Preliminary Responses IND 17627
3/5/08	Email/RACR	Email RACR	Acorda cancels CMC TelCon
3/7/08	Email RACR	Email RACR	FDA request for protocol amendment
3/19/08	Full Submission	Gen Cor	IND Safety Report
3/19/08	Full Submission	Gen Cor	IND Safety Report
3/19/08	Full Submission	Gen Cor	IND Safety Report
3/24/08	Email from The ECG Warehouse	RACR Gen Cor	TQT Study
3/25/08	Full Submission	Gen Cor	Teleconference minutes
3/27/08	Full Submission	Gen Cor	IND Safety Report
4/8/08	Full Submission	Gen Cor	Annual report
4/10/08	Full Submission	Protocol Amendment	Response to FDA Request for Information
4/14/08	Full Submission	Gen Cor	IND Safety Report
4/17/08	Full Submission	Gen Cor	Request for Fast Track Designation
4/18/08	Full Submission	Protocol Amendment	New Investigators MS-F202 EXT
5/12/08	Full Submission	Protocol Amendment	New Investigators MS-F203 EXT
5/13/08	Full Submission	Protocol Amendment	MS-F204
5/15/08	RACR	RACR Email	MS-F204 Study Database Locked
5/19/08	Full Submission	Protocol Amendment	New Investigators MS-F204

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
5/30/08	Full Submission	Gen correspondence	Amendment SAP MS-F202 EXT
6/13/08	Full Submission	Gen correspondence	(SAP) for the (ISS) VERSION 1.0
6/6/08	Full Submission	Gen Cor	IND Safety Report
6/12/08	Full Submission	Gen Cor	FOI Document request
6/13/08	Letter from FOI/FDA	Gen correspondence	acknowledgment of Acorda's FOI Document request
6/13/08	Fax from FDA	FDA Fax response	Fast Track Application
6/13/08	Full Submission	Gen Cor	IND Safety Report
6/13/08	Full Submission	Gen Cor	IND Safety Report
6/19/08	Full Submission	Gen Cor	Request for a type B (pre NDA) meeting
6/23/08	Full Submission	Gen Cor	IND Safety Report
6/27/08	Full Submission	Gen Cor	IND Safety Report
7/3/08	Full Submission	Info Amendment	Final Clinical Reports
7/7/08	Email from FDA and discussion with Acorda	RACR Gen correspondence	Approval Request for Type B Meeting
7/11/08	Full Submission	Protocol Amendment: New Protocol	Protocol FeFa10F-SR-2008
7/22/08	Full Submission	Protocol Amendment	New Investigators MS-F202 EXT
7/24/08	Full Submission	Gen Cor	Population PK and PK/PD Analysis Proposal for Fampridine-SR Tablets
7/25/08	Full Submission	Gen Cor	Request for reconsideration of fast Track Designation
8/4/08	Full Submission	Protocol Amendment	New Investigators MS-F204ext
8/8/08	Full Submission	Protocol Amendment	Change in Protocol
8/20/08	Full Submission	Information Amendment	Pharmacology/ Toxicology
8/21/08	Full Submission	Information Amendment	Clinical

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627			
DATE	MEDIA	TYPE	SUBJECT
8/29/08	Full Submission	Gen Cor	Type B Meeting Briefing Package
9/10/08	Full Submission	Protocol Amendment	New Investigator
9/15/08	Full Submission	RESPONSE TO FDA REQUEST FOR	Information for FDA's QT Study Group
9/19/08	Full Submission	Protocol Amendment	Statistical Analysis Plan (SAP)
10/2/08	Full Submission	Gen Cor	Protocol
10/24/08	Full Submission	Gen Cor	IND Safety Report
10/31/08	Full Submission	Gen Cor	Clinical
11/12/08	Full Submission	Gen Cor	IND Safety Report
11/12/08	Full Submission	Protocol Amendment	New Investigators MS-F202 EXT
11/13/08	Full Submission	Gen Cor	Acorda's Meeting minutes of the 10/27/08 Meeting
11/16/08	RACR	RACR	Type B Meeting Briefing Package
11/17/08			
11/19/08	Full Submission	Gen Cor	Investigator's Brochure for Fampridine SR
12/8/08	Full Submission	Info. Amend.	Pharmacology/Toxicology study reports
12/10/08	Full Submission	Info. Amend.	Amended Clinical study reports
12/23/08	Full Submission	Prot Amend	New Investigators
12/31/08	Fax from FDA	FDA Fax RACR	FDA Official Minutes of Meeting
2009			
1/28/09	Full Submission	Gen Cor	REQUEST FOR PROPRIETY NAME REVIEW
2/6/09	Full Submission	Gen Cor	IND Safety Report
2/25/09	Full Submission	Gen Cor	IND Safety Report
2/23/09	Full Submission	Gen Cor	withdrawal of the REQUEST FOR PROPRIETY NAME REVIEW

Exhibit 11: IND 17,627 Tracking Log

Fampridine SR IND 17 627

DATE	MEDIA	TYPE	SUBJECT
3/18/09	Full Submission	Gen Cor	IND Safety Report
3/27/09	Full Submission	Request for Addiitonal Clinical Information	Additional clin Info on Sites 11, 22 and 33 paper with 3 CD's
4/1/09	Full Submission	Gen Cor	IND Safety Report
4/9/09	FDA Letter to Acorda	Gen Cor	FDA Approval withdrawal of the REQUEST FOR PROPRIETY NAME REVIEW
4/29/09	Full Submission	Gen Cor	Annual report
5/7/09			
5/20/09 (8:30AM)	Compliance	FORM FDA 482 Notice Of Inspection	Notice of Inspection
5/13/09	Full Submission	Info. Amend.	Pharmacology/Toxicology study reports REG-006055 JS_6/4/09
6/5/09	Full Submission	Gen Cor	IND Safety Report
6/15/09	Full Submission	Gen Cor	IND Safety Report
6/16/09	Full Submission	Gen Cor	IND Safety Report
7/9/2009	Full Submission	Gen Cor	Protocol Amendment
7/21/2009	Full Submission	Gen Cor	Protocol Amendment
7/31/09	Full Submission	Gen Cor	Clinical Study Report
8/17/09	Full Submission	Gen Cor	Protocol Amendment
8/28/09	Full Submission	Gen Cor	Protocol Amendment
11/5/09	Full Submission	Gen Cor	Information Amendment
12/17/09	Full Submission	Gen Cor	Protocol Amendment
12/22/09	Full Submission	Gen Cor	Protocol Amendment
1/29/10	Full Submission	Gen Cor	Protocol Amendment

Exhibit 12
NDA 22-250 Tracking Log of Applicant Submissions
(Outgoing Only)

Request Date	Response date	Sequence	Comments
	January 31, 2009	0000	Original submission
	February 6, 2009	0001	Correspondence re: FDA Form 356h
	February 27, 2009	0002	Correspondence re: Propriety Name Review
February 20, 2009	March 10, 2009	0003	Correspondence re: Safety Question Set #1
March 02, 2009	March 13, 2009	0004	Correspondence re: Safety Question Set #2
	March 18, 2009	0005	Correspondence re: Legacy studies
February 23, 2009	March 20, 2009	0006	Correspondence re: Nonclinical
	April 22, 2009	0007	Response to RTF letter
	May 8, 2009	0008	Correspondence re: Proprietary Name review
May 12, 2009	May 15, 2009	0009	Correspondence re: Nonclinical questions
May 14, 2009	May 20, 2009	0010	Correspondence re: Clinical questions
May 14, 2009	May 28, 2009	0011	Correspondence re: Clinical questions
	June 22, 2009	0012	Safety update
	June 24, 2009	0013	Correspondence re: case report forms
May 26, 2009	June 30, 2009	0014	CMC update
July 2, 2009	July 14, 2009	0015	Correspondence re: Clinical Safety
July 2, 2009	July 21, 2009	0016	Correspondence re: Non-Clinical
	July 22, 2009	0017	Correspondence re: efficacy data
July 13, 2009	July 24, 2009	0018	Correspondence re: Clinical
	August 04, 2009	0019	Update re: US agent information
July 13, 2009	August 05, 2009	0020	Correspondence re: Clinical questions
July 08, 2009 (telecom)	August 12, 2009	0021	Correspondence re: Clinical questions
August 07, 2009	August 14, 2009	0022	Correspondence re: Clinical questions
August 17, 2009	August 20, 2009	0023	Correspondence re: Clinical questions
August 19, 2009	September 4, 2009	0024	Correspondence re: Clinical questions
August 25, 2009	September 8, 2009	0025	Correspondence re: Clinical questions
August 28, 2009	September 14, 2009	0026	Correspondence re: Clinical questions
	September 16, 2009	0027	Correspondence re: Proprietary Name Review

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Exhibit 12
NDA 22-250 Tracking Log of Applicant Submissions
(Outgoing Only)

Request Date	Response date	Sequence	Comments
August 27, 2009	September 16, 2009	0028	Correspondence re: Labeling
	September 18, 2009	0029	Correspondence re: CMC
September 18, 2009	September 21, 2009	0030	Correspondence re: Clinical questions
	September 21, 2009	0031	Correspondence re: CMC
	October 20, 2009	0032	Correspondence re: Risk Evaluation and Mitigation Strategy (REMS)
October 23, 2009	October 28, 2009	0033	Correspondence re: Nonclinical questions
	November 23, 2009	0034	Correspondence re: Proprietary Name Review
November 16, 2009	November 25, 2009	0035	Correspondence re: Nonclinical questions
November 20, 2009	December 8, 2009	0036	Correspondence re: USAN
December 3, 2009	December 8, 2009	0037	Correspondence re: USAN
August 13, 2009	December 15, 2009	0038	Correspondence re: CMC
December 10, 2009	December 15, 2009	0039	Correspondence re: Labeling
December 8 and 10, 2009	December 15, 2009	0040	Correspondence re: Labeling
December 23, 2009	December 29, 2009	0041	Correspondence re: Labeling
December 18, 2009	January 6, 2010	0042	Correspondence re: REMS
December 23, 2009	January 6, 2010	0043	Correspondence re: Labeling
	January 8, 2010	0044	Correspondence re: Labeling
December 18, 2009	January 14, 2010	0045	Correspondence re: PMR/PMCs:
January 14, 2010	January 19, 2010	0046	Correspondence re: PMC
January 15, 2010	January 19, 2010	0047	Correspondence re: PMR
January 15, 2010	January 19, 2010	0048	Correspondence re: Labeling
January 13, 2010	January 19, 2010	0049	Correspondence re: REMS
January 19, 2010	January 20, 2010	0050	Correspondence re: PMC
January 19, 2010	January 20, 2010	0051	Correspondence re: REMS
January 19, 2010	January 21, 2010	0052	Correspondence re: PMR
January 21, 2010	January 21, 2010	0053	Correspondence re: Labeling
January 22, 2010			Received FDA approval letter
	February 5, 2010	0054	SPL for Approved NDA 022250